STATUTORY INSTRUMENTS

2012 No. 1916

The Human Medicines Regulations 2012

PART 5

Marketing authorisations

Application of this Part

48.—(1) This Part applies to relevant medicinal products.

(2) In this Part—

"generic medicinal product" has the meaning given in Article 10(2)(b) of the 2001 Directive;

"relevant medicinal product" means a medicinal product that is not—

(a) a registrable homoeopathic medicinal product; or

(b) a traditional herbal medicinal product; and

"reference medicinal product" has the meaning given in Article 10(2)(a) of the 2001 Directive.

Application for UK marketing authorisation

Application for grant of UK marketing authorisation

49.—(1) The licensing authority may, subject to regulation 58, grant a UK marketing authorisation for a relevant medicinal product in response to an application made in accordance with this Part.

(2) A marketing authorisation granted under paragraph (1) shall contain terms approved by the licensing authority.

(3) The applicant must be established in the European Union.

(4) The application must be—

(a) made in writing;

(b) signed by or on behalf of the applicant; and

(c) unless the licensing authority directs otherwise, accompanied by any fee payable in connection with the application.

(5) An application is treated as signed for the purposes of paragraph (4)(b) if it is signed with an electronic signature.

(6) The application and any accompanying material must be in English.

(7) The application must include a statement indicating whether the product to which the application relates should be available—

(a) only on prescription;

(b) only from a pharmacy; or

(c) on general sale.

(8) The application must include a statement indicating—

(a) whether any terms of the authorisation are proposed relating to the method of sale or supply of the product (including, in particular, any proposed restrictions affecting the circumstances of the use or promotion of the product); and

(b) if so, what terms are proposed.

Accompanying material

50.—(1) An applicant for the grant of a UK marketing authorisation for a relevant medicinal product must provide the material specified in Schedule 8 in relation to the product.

(2) An applicant for the grant of a UK marketing authorisation for a radionuclide generator must, in addition, provide—

(a) a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation; and

(b) qualitative and quantitative particulars of the eluate or the sublimate.

(3) The applicant must also, if requested by the licensing authority to do so, provide the licensing authority with material or information that the licensing authority reasonably considers necessary for dealing with the application.

(4) If any of the medicinal products to which the application relates is liable to be imported from a country other than an EEA State, the material or information referred to in paragraph (3) may include an undertaking from the manufacturer of the product to comply with the matters set out in Schedule 9.

(5) Material that is submitted under this regulation must be submitted in accordance with the applicable provisions of Annex I to the 2001 Directive.

(6) This regulation is subject to—

(a) regulation 51 (applications relating to generic medicinal products);

(b) regulation 52 (applications relating to certain medicinal products that do not qualify as generic etc);

(c) regulation 53 (applications relating to certain biological medicinal products);

(d) regulation 54 (applications relating to products in well-established medicinal use);

(e) regulation 55 (applications relating to new combinations of active substances);

(f) regulation 56 (applications containing information supplied in relation to another medicinal product with consent); and

(g) Schedule 10 (applications relating to national homoeopathic products).

Applications relating to generic medicinal products

51.—(1) An applicant for a UK marketing authorisation for a relevant medicinal product that is a generic medicinal product may provide information in relation to the application in accordance with Article 10(1), (5) and (6) of the 2001 Directive.

(2) If the licensing authority grants a UK marketing authorisation for the generic medicinal product in accordance with paragraph (1), it is a term of the authorisation that the product must not be sold or supplied, or offered for sale or supply, in the United Kingdom before the time at which it may be placed on the market in accordance with—

(a) Article 10(1) of the 2001 Directive; or

(b) in a case where the application for the marketing authorisation for the reference medicinal product referred to in the application was submitted on or before 30th October 2005, Article 10(1) of the 2001 Directive as it stood before it was amended by Article 1(8) of Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending the 2001 Directive(**1**) ("Directive 2004/27/EC"), in accordance with Article 2 of Directive 2004/27/EC .

Applications relating to certain medicinal products that do not qualify as generic etc

52.—(1) This regulation applies where—

(a) an application is made for a UK marketing authorisation in respect of a product by reference to another medicinal product as reference medicinal product; and

(b) one or more of the circumstances listed in Article 10(3) of the 2001 Directive applies in respect of the application.

(2) The applicant must provide information in accordance with Article 10(3) and (6) of the 2001 Directive.

(3) Regulation 51(2) shall apply to the application as it applies in relation to an application made in accordance with regulation 51(1).

Applications relating to similar biological medicinal products

53.—(1) This regulation applies if an applicant for a UK marketing authorisation for a biological medicinal product is not able to show that it meets a condition for its being a generic version of a similar medicinal product because of any of the reasons described in Article 10(4) of the 2001 Directive.

(2) The applicant must provide information in accordance with Article 10(4) and (6) of the 2001 Directive.

(3) Regulation 51(2) shall apply to the application as it applies in relation to an application made in accordance with regulation 51(1).

Applications relating to products in well-established medicinal use

54.—(1) This regulation applies if an applicant for a UK marketing authorisation for a relevant medicinal product is able to demonstrate that the active substances of the product have been in well-established medicinal use within the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I to the 2001 Directive.

(2) The applicant must provide information in accordance with Article 10a of the 2001 Directive.

Applications relating to new combinations of active substances

55.—(1) This paragraph applies to an application for a UK marketing authorisation for a relevant medicinal product that contains active substances that—

(a) have been used in medicinal products that have been the subject of a marketing authorisation under these Regulations, the 2001 Directive or Regulation (EC) No 726/2004; but

(b) have not been used in that combination for therapeutic purposes.

(2) The applicant must provide information in accordance with Article 10b of the 2001 Directive.

(**1**) OJ No L 136, 30.4.2004, p. 34.

Applications containing information supplied in relation to another product with consent

56.—(1) This regulation applies to an application for a UK marketing authorisation for a relevant medicinal product where—

(a) the product that is the subject of the application ("product A") has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as a product ("product B");

(b) product B is the subject of a UK marketing authorisation; and

(c) the holder of the marketing authorisation for product B has allowed use to be made of the pharmaceutical, pre-clinical and clinical documentation contained in the file on product B with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

(2) The documentation referred to in paragraph (1)(c) in relation to product B may be used in relation to the application in relation to product A, in accordance with Article 10c of the 2001 Directive.

Obligation to update information supplied in connection with application

57.—(1) The applicant for a UK marketing authorisation must update information supplied in accordance with paragraphs 18 to 21 of Schedule 8 (material to accompany an application for a UK marketing authorisation) in connection with the application.

(2) The applicant must update information supplied in connection with the application to include any further information that is relevant to the evaluation of the safety, quality or efficacy of the product concerned.

(3) Updated information within paragraphs (1) or (2) must be provided as soon as is reasonably practicable after the applicant becomes aware of it.

Consideration of application

Consideration of application

58.—(1) The licensing authority must take all reasonable steps to ensure that it makes a decision to grant or refuse a UK marketing authorisation before the end of 210 days beginning immediately after the day on which the application for the authorisation is submitted in accordance with regulations 49 to 55.

(2) If the licensing authority requests the applicant to provide any further information or material, the period referred to in paragraph (1) is suspended for the period—

(a) beginning with the date on which the request is made; and

(b) ending with the date on which the information or material is provided.

(3) If the licensing authority requests the applicant to give an oral or written explanation of the application, the period referred to in paragraph (1) is suspended for the period—

(a) beginning with the date on which the request is made; and

(b) ending with the date on which the explanation is provided.

(4) The licensing authority may grant the application only if, having considered the application and the accompanying material, the authority thinks that—

(a) the applicant has established the therapeutic efficacy of the product to which the application relates;

(b) the positive therapeutic effects of the product outweigh the risks to the health of patients or of the public associated with the product;

(c) the application and the accompanying material complies with regulations 49 to 55; and

(d) the product's qualitative and quantitative composition is as described in the application and the accompanying material.

(5) Schedule 11 makes provision about advice and representations in relation to an application for the grant of a UK marketing authorisation.

(6) This regulation does not apply to an application that—

(a) has been submitted to the licensing authority in accordance with Article 28 of the 2001 Directive; or

(b) has been referred to the Committee for Medicinal Products for Human Use established under Regulation (EC) No 726/2004 for the application of the procedure laid down in Articles 32 to 34 of the 2001 Directive.

(7) An application to which paragraph (6) applies is to be determined by the licensing authority in accordance with Chapter 4 of Title III of the 2001 Directive.

Conditions of UK marketing authorisation: general

59.—(1) The licensing authority may—

(a) grant a UK marketing authorisation subject to one or more of the conditions in paragraph (2); or

(b) vary or remove a condition in paragraph (2) to which the UK marketing authorisation is subject.

(2) Those conditions are—

(a) to take certain measures for ensuring the safe use of the medicinal product and include them in the risk management plan;

(b) to conduct post-authorisation safety studies;

(c) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Part 11;

(d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

(e) the existence of an adequate pharmacovigilance system; and

(f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed.

(3) An obligation to conduct such studies as are referred to in paragraph (2)(f) must be based on the delegated acts adopted pursuant to Article 22b of the 2001 Directive, while taking into account the scientific guidance referred to in Article 108a of the 2001 Directive.

(4) The marketing authorisation must lay down deadlines for the fulfilment of the conditions in paragraph (2) where necessary.

(5) The licensing authority must notify the EMA of any marketing authorisation that it has granted subject to a condition included in accordance with this regulation.

(6) The holder of the authorisation must incorporate any condition included in a marketing authorisation in accordance with this regulation into the risk management system for the product.

(7) Schedule 11 makes provision about advice and representations in relation to proposals to vary or remove a condition to which a UK marketing authorisation is subject.

Conditions of UK marketing authorisation: exceptional circumstances

60.—(1) The licensing authority may—

(a) grant a UK marketing authorisation subject to conditions in accordance with the following paragraphs of this regulation; or

(b) vary or remove such a condition to which the UK marketing authorisation is subject.

(2) The powers in paragraph (1) may be exercised only after consultation with the applicant for the authorisation or (as the case may be) its holder.

(3) The power in paragraph (1)(a) to grant an authorisation subject to conditions may be exercised only—

(a) in exceptional circumstances; and

(b) when the applicant can show that the applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use.

(4) The conditions must relate to a matter addressed by Annex I to the 2001 Directive.

(5) The conditions may, in particular, relate to the safety of the product to which the authorisation relates.

(6) The conditions may, in particular, require that, where there is a serious adverse reaction relating to the use of the product—

(a) the reaction must be reported to the licensing authority; and

(b) such other action as may be specified in the conditions must be taken.

(7) The licensing authority must keep under review—

(a) the conditions under this regulation to which a UK marketing authorisation is subject; and

(b) the holder's compliance with those conditions.

(8) The licensing authority must consider those matters no less frequently than—

(a) at the end of the period of one year beginning with the date on which the authorisation was granted; and

(b) at the end of each subsequent period of one year.

(9) The licensing authority must notify the EMA of any marketing authorisation that it has granted subject to a condition included in accordance with this regulation.

(10) The holder of the authorisation must incorporate any condition included in a marketing authorisation in accordance with this regulation into the risk management system for the product.

(11) Schedule 11 makes provision about advice and representations in relation to proposals to vary or remove a condition to which a UK marketing authorisation is subject.

Conditions of UK marketing authorisation: new obligations post-authorisation

61.—(1) After the granting of a UK marketing authorisation, the licensing authority may impose an obligation on the holder of the authorisation in accordance with either or both of —

(a) paragraph (4), in a case where paragraph (2) applies; or

(b) paragraph (5), in a case where paragraph (3) applies.

(2) This paragraph applies if there are concerns about the risks of a medicinal product that is the subject of a marketing authorisation.

(3) This paragraph applies if the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.

(4) The obligation in this paragraph is to conduct a post-authorisation safety study.

(5) The obligation in this paragraph is to conduct a post-authorisation efficacy study.

(6) If concerns as described in paragraph (2) apply to more than one medicinal product, the licensing authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study.

(7) The obligation under paragraph (5) shall be based on the delegated acts adopted pursuant to Article 22b of the 2001 Directive while taking account of the scientific guidance referred to in Article 108a of the 2001 Directive.

(8) Where the licensing authority imposes an obligation under paragraph (4) or (5), it must without delay give written notice to the holder of —

(a) the imposition of the obligation;

(b) the justification for the imposition;

(c) the objectives and timeframe for submission and conduct of the study; and

(d) the opportunity to present written observations in accordance with paragraph (9) and the time limit specified for doing so.

(9) Where the holder so requests within the period of thirty days beginning on the day after the receipt by the holder of the notice referred to in paragraph (8), the licensing authority must provide the holder of the authorisation with an opportunity to present written observations in response to the imposition of the obligation within the time limit specified by the licensing authority in the notice.

(10) Where the holder presents written observations under paragraph (9), the licensing authority must withdraw or confirm the imposition of the obligation under paragraph (4) or (5) on the basis of the written observations as soon as is reasonably practicable.

(11) Paragraph (12) applies where the licensing authority—

(a) imposes an obligation under paragraph (4) or (5) and the holder does not present written representations under paragraph (9); or

(b) confirms the imposition of an obligation under paragraph (10).

(12) Where this paragraph applies, the licensing authority must vary the marketing authorisation to include the obligation as a condition of the marketing authorisation as if it were a condition imposed under regulation 59 (conditions of UK marketing authorisations: general).

(13) The licensing authority must notify the EMA that the marketing authorisation is subject to a condition included in accordance with paragraph (12).

(14) The holder of the authorisation must incorporate any condition included in a marketing authorisation in accordance with paragraph (12) into the risk management system for the product.

(15) Schedule 11, which makes provision about advice and representations in relation to proposals to vary or remove a condition to which a UK marketing authorisation is subject, shall apply in relation to the variation or removal of a condition included in a marketing authorisation in accordance with paragraph (12).

Classification of UK marketing authorisation

62.—(1) A UK marketing authorisation must include a term that the product to which the authorisation relates is to be available—

(a) only on prescription;

(b) only from a pharmacy; or

(c) on general sale.

(2) In making a determination under paragraph (1), the licensing authority must have regard to the following in relation to the product—

(a) the maximum single dose;

(b) the maximum daily dose;

(c) the strength of the product;

(d) its pharmaceutical form;

(e) its packaging; and

(f) such other circumstances relating to its use as the licensing authority considers relevant.

(3) A UK marketing authorisation must be granted subject to a condition that the product to which the authorisation relates is to be available only on prescription if the licensing authority considers that the product—

(a) is likely to present a direct or indirect danger to human health, even when used correctly, if used without the supervision of a doctor or dentist;

(b) is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health;

(c) contains substances, or preparations of substances, of which the activity requires, or the side effects require, further investigation; or

(d) is normally prescribed by a doctor or dentist for parenteral administration.

(4) In deciding whether paragraph (3) applies to a product, the licensing authority must take into account whether the product—

(a) contains a substance listed in any of Schedules I, II or IV to the Narcotics Drugs Convention (where the product is not a preparation listed in Schedule III to that Convention);

(b) contains a substance listed in any of Schedules I to IV of the Psychotropic Substances Convention (where the product is not a preparation which may be exempted from measures of control in accordance with paragraphs 2 and 3 of article 3 of that Convention);

(c) is likely, if incorrectly used—

(i) to present a substantial risk of medicinal abuse,

(ii) to lead to addiction, or

(iii) to be used for illegal purposes;

(d) contains a substance that, by reason of its novelty or properties, might fall within paragraph (c), but as to which there is insufficient information available to determine whether it does so fall;

(e) by reason of its pharmaceutical characteristics or novelty, or in the interests of public health, is reserved for treatments that can only be followed in a hospital;

(f) is used in the treatment of conditions that must be diagnosed in a hospital or in an institution with special diagnostic facilities (although administration and subsequent supervision may be carried out elsewhere); or

(g) is intended for outpatients but may produce very serious side effects which would require a prescription drawn up as required by a specialist and special supervision throughout the treatment.

(5) A UK marketing authorisation may include a term that the product to which the authorisation relates is to be available on general sale only if the licensing authority considers that the product can with reasonable safety be sold or supplied otherwise than by, or under the supervision of, a pharmacist.

Frequency of periodic safety update reports

63.—(1) The licensing authority must, if paragraph (2) applies, include in a UK marketing authorisation a term that specifies the frequency, calculated from the date on which the authorisation is granted, with which the holder of the authorisation must submit periodic safety update reports in accordance with regulation 191(8) (obligation on holder to submit periodic safety update reports: general requirements).

(2) This paragraph applies in the case of a medicinal product in relation to which regulation 191(8) applies by virtue of regulation 191(1).

Duties of licensing authority in connection with determination

64.—(1) This regulation applies if the licensing authority grants a UK marketing authorisation.

(2) The licensing authority must inform the holder of the authorisation of the summary of the product characteristics as approved by the authority.

(3) The licensing authority must ensure that the summary of the product characteristics continues to match the version it has approved, subject to any changes it approves.

(4) As soon as is reasonably practicable after granting the marketing authorisation, the licensing authority must make available publicly—

(a) the marketing authorisation;

(b) the package leaflet;

(c) the summary of the product characteristics;

(d) any conditions established in accordance with Articles 21a, 22 and 22a of the 2001 Directive; and

(e) any deadlines for the fulfilment of those conditions.

(5) The licensing authority must draw up an assessment report and make comments on the file as regards—

(a) the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the product to which the authorisation relates; or

(b) in the case of a national homoeopathic medicinal product within the meaning of Schedule 10, the information submitted under paragraphs 3 to 5 of that Schedule.

(6) The licensing authority must—

(a) revise the assessment report whenever new information becomes available that is of importance for the evaluation of the quality, safety or efficacy of the medicinal product;

(b) make the assessment report publicly available (with the omission of information of a commercially confidential nature) as soon as is reasonably practicable after it has been prepared or revised; and

(c) include in the assessment report a summary, written in a manner that is understandable to the public, that contains, in particular, a section relating to the conditions of use of the medicinal product.

(7) The assessment must be provided separately for each indication that is authorised.

Validity of UK marketing authorisation

Validity of UK marketing authorisation

65.—(1) Subject to the following paragraphs, a UK marketing authorisation remains in force—

(a) for an initial period of five years beginning with the date on which it is granted; and

(b) if the authorisation is renewed in accordance with regulation 66, for an unlimited period after its renewal.

(2) The licensing authority may, on the first application for renewal of an authorisation, determine on grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, that it should be necessary for the holder to make one further application for renewal.

(3) In that event the authorisation remains in force—

(a) for a further period of five years beginning with the date on which it is first renewed; and

(b) if the authorisation is further renewed under regulation 66, for an unlimited period after its further renewal.

(4) If an application for the renewal or further renewal of an authorisation is made in accordance with regulation 66 the authorisation remains in force until the licensing authority notifies the applicant of its decision on the application.

(5) This regulation is subject to—

(a) regulation 67 (failure to place on the market etc); and

(b) regulation 68 (revocation etc of marketing authorisations).

Application for renewal of authorisation

66.—(1) The licensing authority may renew a UK marketing authorisation in response to an application made in accordance with this regulation.

(2) The applicant must be established in the European Union.

(3) The application must be—

(a) made in writing;

(b) signed by or on behalf of the applicant; and

(c) unless the licensing authority directs otherwise, accompanied by any fee payable in connection with the application.

(4) An application is treated as signed for the purposes of paragraph (3)(b) if it is signed with an electronic signature.

(5) The application must be made so that it is received by the licensing authority before the beginning of the period of nine months ending with the expiry of the period mentioned in paragraph (1)(a) or (as the case may be) (3)(a) of regulation 65 (initial and further period of validity).

(6) The holder must provide a consolidated version of the file in respect of quality, safety and efficacy, including—

(a) the evaluation of data contained in suspected adverse reaction reports and periodic safety update reports submitted in accordance with Part 11; and

(b) all amendments made since the authorisation was granted.

(7) The licensing authority may renew a UK marketing authorisation only if, having considered the application and the material accompanying it, the authority thinks that the positive therapeutic

effects of the product to which the authorisation relates outweigh the risks of the product to the health of patients or of the public.

(8) Schedule 11 makes provision about advice and representations in relation to an application for the renewal of a UK marketing authorisation.

Failure to place on the market etc

67.—(1) A UK marketing authorisation ceases to be in force if the product to which it relates is not placed on the market in the United Kingdom during the period of three years beginning immediately after the day on which it was granted.

(2) A UK marketing authorisation for a product which has been placed on the market ceases to be in force if the product to which it relates is not sold or supplied in the United Kingdom for a period of three years.

(3) This regulation does not apply if the licensing authority grants an exemption from its operation.

(4) An exemption may be granted—

(a) in response to an application in writing by the holder of the UK marketing authorisation; or

(b) by the licensing authority of its own motion.

(5) An exemption may be granted only—

(a) in exceptional circumstances; and

(b) on public health grounds.

(6) An exemption—

(a) has effect for the period determined by the licensing authority, which may not exceed three years beginning with the day on which it is granted; and

(b) may be renewed or further renewed.

Revocation, variation and suspension of marketing authorisation

Revocation, variation and suspension of UK marketing authorisation

68.—(1) The licensing authority may revoke, vary or suspend a UK marketing authorisation if any of the following conditions is met.

(2) Condition A is that the licensing authority thinks that—

(a) the product to which the authorisation relates is harmful;

(b) the positive therapeutic effects of the product do not outweigh the risks of the product to the health of patients or of the public;

(c) the product lacks therapeutic efficacy, in that therapeutic results cannot be obtained from the product; or

(d) the product's qualitative or quantitative composition is not as described in the application for the authorisation or the material supplied with it.

(3) Condition B is that the licensing authority thinks that the application or the material supplied with it is incorrect.

(4) Condition C is that the licensing authority thinks that there has been a breach of—

(a) a term of the authorisation; or

(b) a requirement imposed by Part 13 (packaging and leaflets).

(5) Condition D is that the licensing authority thinks that a condition to which the authorisation is subject by virtue of regulations 59 (conditions of UK marketing authorisations: general), 60 (conditions of UK marketing authorisations: exceptional circumstances) or 61 (conditions of UK marketing authorisations: new obligations post-authorisation) has not been fulfilled.

(6) Condition E is that the licensing authority thinks that the holder of the authorisation has not complied with regulation 75(1) to (3) (requirements to provide information).

(7) Condition F is that the holder of the authorisation has ceased to be established in the European Union.

(8) Condition G is that—

(a) the product to which the authorisation relates is manufactured in the United Kingdom; and

(b) the licensing authority thinks that the holder of the manufacturer's licence for the product has failed to comply in relation to the product with regulations 37 (manufacturing and assembly), 38 (imports from states other than EEA States), 39 (further requirements for manufacturer's licence), 40 (obligation to provide information relating to control methods) or 41 (requirements as to qualified persons).

(9) Condition H is that—

(a) the product to which the authorisation relates is manufactured in a member State other than the United Kingdom; and

(b) the licensing authority thinks that the licensee under the manufacturer's licence for the product has failed to comply in relation to the product with provision giving effect to Article 41 of the 2001 Directive (requirements relating to manufacturing authorisations) in that member State.

(10) Condition I is that the licensing authority thinks that urgent action to protect public health is necessary, in which case it—

(a) may suspend the authorisation; and

(b) must notify the suspension to the EMA, the European Commission, and all other member States by the end of the next working day following the day on which the suspension comes into force.

(11) Condition J is that—

(a) the holder applies to vary the authorisation; and

(b) the licensing authority thinks that the application should be granted.

(12) Schedule 11 makes provision about advice and representations in relation to a proposal to revoke, vary or suspend a UK marketing authorisation, other than a proposal to vary an authorisation on the application of its holder.

(13) This regulation is subject to regulation 70 (authorisations granted under Chapter 4 of Title III of the 2001 Directive).

Suspension of use etc of relevant medicinal product

69.—(1) The licensing authority may, if any of the following conditions are met, suspend the use, sale, supply or offer for sale or supply within the United Kingdom of a product to which a UK marketing authorisation relates.

(2) Condition A is that the licensing authority thinks that—

(a) the product to which the authorisation relates is harmful;

(b) the positive therapeutic effects of the product do not outweigh the risks of the product to the health of patients or of the public;

(c) the product lacks therapeutic efficacy, in that therapeutic results cannot be obtained from the product; or

(d) the product's qualitative or quantitative composition is not as described in the application for the authorisation or the material supplied with it.

(3) Condition B is that the licensing authority thinks that the holder of the authorisation has not complied with regulation 75(7) (requirements to provide proof of controls on manufacturing process).

(4) Condition C is that the licensing authority thinks that there has been a breach of—

(a) a term of the authorisation; or

(b) a requirement imposed by Part 13 (packaging and leaflets).

(5) Condition D is that the licensing authority thinks that paragraph (4) or (5) of regulation 26 (power to revoke, suspend or vary manufacturers' licences) applies in relation to the manufacturer's licence for the product to which the authorisation relates.

(6) A suspension under this regulation may relate to batches of the product.

(7) The licensing authority must give notice in writing of a suspension under this regulation to the holder of the UK marketing authorisation.

(8) The licensing authority must provide in the notice that the suspension—

(a) is to take effect immediately or from a date specified in the notice; and

(b) is to apply for the period specified in the notice.

(9) Where a medicinal product is the subject of a suspension under this regulation, the licensing authority may—

(a) in exceptional circumstances; and

(b) for such a transitional period as the licensing authority may determine,

allow the supply of the medicinal product to patients who are already being treated with the medicinal product.

(10) This regulation is subject to regulation 70 (authorisations granted under Chapter 4 of Title III of the 2001 Directive).

Authorisations granted under Chapter 4 of Title III of the 2001 Directive

70.—(1) Regulations 68 and 69 do not apply in relation to a UK marketing authorisation that—

(a) was granted in accordance with the provisions of Chapter 4 of Title III of the 2001 Directive (mutual recognition procedure and decentralised procedure);

(b) was granted before 1st January 1995 in accordance with Article 4 of Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology(**2**); or

(c) was subject to the procedure laid down in Articles 32 to 34 of the 2001 Directive following a referral under Article 30 or 31 of that Directive, unless the procedure was limited to certain specific parts of the authorisation.

(2) A proposal by the licensing authority to vary, suspend or revoke a marketing authorisation within paragraph (1), or an application by the holder of such an authorisation to vary or revoke it, is to be determined in accordance with Chapter 4 of Title III of the 2001 Directive.

(**2**) OJ No L 15, 17.1.1987. p.38.

Withdrawal of medicinal product from the market

71.—(1) This regulation applies if—

(a) under regulation 68, regulation 70(2), Article 34(3) of the 2001 Directive or Regulation (EC) No 726/2004 the licensing authority or the European Commission revokes or suspends a marketing authorisation, or

(b) under regulation 69 or Article 20(4) of Regulation (EC) No 726/2004 the licensing authority suspends the use, sale, supply or offer for sale or supply within the United Kingdom of a product to which a marketing authorisation relates.

(2) The licensing authority may give written notice to the person who is, or immediately before its revocation was, the holder of the authorisation requiring that person to comply with both of the following requirements.

(3) Requirement A is to take all reasonably practicable steps to inform wholesalers, retailers, medical practitioners, patients and others who may be in possession of the product to which the authorisation relates of—

(a) the revocation or suspension;

(b) the reasons for the revocation or suspension; and

(c) any action to be taken to restrict or prevent further use, sale, supply or offer for sale or supply of the product.

(4) Requirement B is to take all reasonably practicable steps to withdraw from the market in the United Kingdom and recover possession of—

(a) the product; or

(b) the batches of the product specified in the notice,

within the time and for the period specified in the notice.

Sale etc of suspended medicinal product

72.—(1) This regulation applies if the use, sale, supply or offer for sale or supply of a medicinal product is suspended in accordance with regulation 69 or 70(2) or Article 20(4) of Regulation (EC) No 726/2004.

(2) A person must not—

(a) sell, supply or offer to sell or supply the product; or

(b) procure the sale, supply or offer for sale or supply of the product,

knowing, or having reasonable cause to believe, that such use, sale, supply or offer for sale or supply is suspended.

Obligations of holder of marketing authorisation

Obligation to notify placing on the market etc

73.—(1) The holder of a UK marketing authorisation must notify the licensing authority of the date on which the product to which the authorisation relates is placed on the market in the United Kingdom, taking account of the various presentations authorised.

(2) A notification under paragraph (1) must be given before the end of the period of two months beginning with the date on which the product is placed on the market.

(3) The holder of a UK marketing authorisation must notify the licensing authority if the product to which the authorisation relates is to be withdrawn from the market in the United Kingdom (whether temporarily or permanently).

(4) A notification under paragraph (3) must be given before the beginning of the period of two months ending with the date on which the product is to be withdrawn from the market unless it is not reasonably practicable to do so.

(5) In that event, the notification must be given as far as is reasonably practicable in advance of the date on which the product is withdrawn from the market.

(6) The licensing authority may require the holder of a UK marketing authorisation to provide—

(a) information relating to the volume of sales in the United Kingdom of the product to which the authorisation relates; or

(b) information of which the holder is aware relating to the volume of prescriptions in the United Kingdom for the product.

(7) The holder of a UK marketing authorisation must provide the licensing authority with information that it requires under paragraph (6)—

(a) where the period within which the information must be provided is specified in a written notice given to the holder by the licensing authority, before the end of that period; or

(b) otherwise, as soon as is reasonably practicable after receipt of the request.

Obligation to take account of scientific and technical progress

74.—(1) The holder of a UK marketing authorisation must keep under review the methods of manufacture and control of the product to which the authorisation relates, taking account of scientific and technical progress.

(2) As soon as is reasonably practicable after becoming aware of the need to do so, the holder must apply to vary the marketing authorisation to make any changes to those methods that are required to ensure they are generally accepted scientific methods.

Obligation to provide information relating to safety etc

75.—(1) The holder of a UK marketing authorisation must provide the licensing authority with any new information that might entail the variation of the authorisation.

(2) The holder must, in particular, provide the licensing authority with the following information—

(a) information about any prohibition or restriction imposed in relation to the product to which the authorisation relates by the competent authority of any country in which the product is on the market;

(b) positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation;

(c) data on the use of the medicinal product where such use is outside the terms of the marketing authorisation; and

(d) any other information that the holder considers might influence the evaluation of the benefits and risks of the product.

(3) Information within paragraph (1) or (2) must be provided as soon as is reasonably practicable after the holder becomes aware of it.

(4) The licensing authority may require the holder of a UK marketing authorisation to provide the authority with information that—

(a) is specified by the licensing authority; and

(b) demonstrates that the positive therapeutic effects of the product to which the authorisation relates continue to outweigh the risks of the product to the health of patients or of the public.

(5) The information that may be required under paragraph (4) includes information arising from use of the product—

(a) in a country which is not an EEA State; or

(b) outside the terms of the marketing authorisation,

including use in clinical trials.

(6) If the information supplied under paragraph (1), (2) or (4) entails the variation of the UK marketing authorisation, the holder must make an application to the licensing authority to that effect as soon as is reasonably practicable after becoming aware of the information.

(7) The licensing authority may require the holder of a UK marketing authorisation to provide the authority with proof of the control methods employed by the manufacturer of the product to which the authorisation relates.

(8) The holder of a UK marketing authorisation must provide the licensing authority with information it requests under paragraphs (4) or (7)—

(a) where the period within which the information must be provided is specified in a written notice given to the holder by the licensing authority, before the end of that period; or

(b) otherwise, as soon as is reasonably practicable after receipt of the request.

Obligation in relation to product information

76.—(1) The holder of a UK marketing authorisation for a medicinal product must ensure that the product information relating to the product is kept up to date with current scientific knowledge.

(2) In this regulation "current scientific knowledge" includes the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

Record-keeping obligations

77. The holder of a marketing authorisation must keep any documents or information that will facilitate the withdrawal or recall from sale or supply of any product to which the authorisation relates.

Obligation to ensure appropriate and continued supplies

78. The holder of a marketing authorisation must take all reasonable steps to ensure appropriate and continued supplies of the product to which the authorisation relates to pharmacies and persons authorised to supply the product so that the needs of patients in the United Kingdom are met.

Offences relating to specific requirements

Failure to provide information on marketing authorisations to EMA

79.—(1) The holder of a marketing authorisation is guilty of an offence if the holder—

(a) has not submitted information to the EMA as required by Article 57(2)(b) of Regulation (EC) No 726/2004 (information on all existing medicinal products for human use

authorised or registered in the EU) in relation to any medicinal product that is the subject of a marketing authorisation granted before 2nd July 2012; and

(b) fails to do so as soon as is reasonably practicable after the coming into force of these Regulations.

(2) The holder of a marketing authorisation is guilty of an offence if the holder fails to submit information to the EMA as required by Article 57(2)(c) of Regulation (EC) No 726/2004 (information on any new or varied authorisations granted in the EU) in relation to any medicinal product that is the subject of a marketing authorisation granted on or after 2nd July 2012 as soon as is reasonably practicable after the grant of the authorisation.

Urgent safety restrictions

80. The holder of a marketing authorisation is guilty of an offence if the holder —

(a) fails to inform the licensing authority or the European Commission in accordance with Article 22(1) of Regulation (EC) No 1234/2008 that the holder has taken urgent safety restrictions on the holder's own initiative;

(b) fails to implement an urgent safety restriction imposed on the holder by the licensing authority or the European Commission under Article 22(2) of that Regulation; or

(c) fails to submit an application for variation of the marketing authorisation to the licensing authority or the European Commission in accordance with Article 22(3) of that Regulation before the end of a period of fifteen days beginning on the day after—

(i) the taking under Article 22(1) or, as the case may be,

(ii) the imposition under Article 22(2),

of that Regulation of an urgent safety restriction.

Offences relating to EU marketing authorisations

Obligation to update information supplied in connection with EU application

81. An applicant for an EU marketing authorisation is guilty of an offence if that person fails to supply updated information to the EMA in accordance with Article 8(3) of the 2001 Directive as applied by Article 6(1) of Regulation (EC) No 726/2004.

EU marketing authorisations: failure to notify placing on market etc

82.—(1) The holder of an EU marketing authorisation is guilty of an offence if the holder fails to notify the EMA in accordance with—

(a) the first paragraph of Article 13(4) of Regulation (EC) No 726/2004 (requirement to notify date of placing of product on the market); or

(b) the second paragraph of Article 13(4) of Regulation (EC) No 726/2004 (requirement to notify that product is to be withdrawn from the market).

(2) The holder of an EU marketing authorisation is guilty of an offence if the holder fails to provide the EMA with information that it requires under the third paragraph of Article 13(4) of Regulation (EC) No 726/2004 (information as to sales and prescriptions)—

(a) where the period within which the information must be provided is specified in a written notice given to the holder by the EMA, before the end of that period; or

(b) otherwise, as soon as is reasonably practicable after receipt of the request.

EU marketing authorisations: failure to take account of technical and scientific progress

83. The holder of an EU marketing authorisation is guilty of an offence if the holder fails to apply to vary the marketing authorisation as required by Article 16(1) of Regulation (EC) No 726/2004 (obligation to take account of scientific and technical progress).

EU marketing authorisations: failure to provide information as to safety etc

84.—(1) The holder of an EU marketing authorisation is guilty of an offence if the holder fails to provide information to the EMA, the Commission or the licensing authority as required by Article 16(2) of Regulation (EC) No 726/2004 (new information which might entail amendment of particulars or documents) as soon as is reasonably practicable after becoming aware of the information.

(2) The holder of an EU marketing authorisation is guilty of an offence if the holder fails to provide the EMA with information that it requests as required by the first paragraph of Article 16(4) of Regulation (EC) No 726/2004 (data on risk-benefit balance).

EU marketing authorisations: failure to update product information

85.—(1) The holder of an EU marketing authorisation for a medicinal product is guilty of an offence if the holder fails to ensure that the product information relating to the product is kept up to date with current scientific knowledge, as required by Article 16(3) of Regulation (EC) No 726/2004.

(2) In this regulation "current scientific knowledge" includes the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

EU marketing authorisations: breach of pharmacovigilance condition etc

86.—(1) The holder of an EU marketing authorisation is guilty of an offence if the holder fails to comply with—

(a) any obligation to which the marketing authorisation is subject by virtue of Articles 10a(1) or 14(7); or

(b) any condition to which the authorisation is subject by virtue of Article 14(8),

of Regulation (EC) No 726/2004.

(2) The holder of an EU marketing authorisation is guilty of an offence if the holder fails to incorporate into the risk management system for the product as required by Article 14a of Regulation (EC) No 726/2004—

(a) any recommendation referred to in Article 9(4)(c), (ca), (cb) or (cc);

(b) any obligation to which the authorisation is subject by virtue of Articles 10a(1) or 14(7) ; or

(c) any condition to which the marketing authorisation is subject by virtue of Article 14(8),

of Regulation (EC) No 726/2004.

Offences relating to advanced therapy medicinal products

Offences in connection with risk management systems and traceability systems

87.—(1) The holder of an EU marketing authorisation for an advanced therapy medicinal product is guilty of an offence if the holder fails to—

(a) submit an additional report evaluating the effectiveness of a risk management system and the results of studies within the period of 21 days beginning on the day following receipt

of a request made under the second sub-paragraph of Article 14(2) of Regulation (EC) No 1394/2007, or such longer period as the EMA may specify; or

(b) include in any periodic safety update report referred to in Article 28(2) of Regulation (EC) No 726/2004 an evaluation of the effectiveness of a risk management system or of the results of any study performed pursuant to the first sub-paragraph of Article 14(2) of Regulation (EC) No 1394/2007, as required by the third sub-paragraph of Article 14(2).

(2) A person who is, or who immediately before its revocation or withdrawal was, the holder of an EU marketing authorisation for an advanced therapy medicinal product is guilty of an offence if the person fails to—

(a) establish and maintain a traceability system in accordance with the requirements set out in Article 15(1) of Regulation (EC) No 1394/2007;

(b) where the product contains human cells or tissues, to ensure that the traceability system is complementary to and compatible with the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC, as regards human cells and tissues other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC, as regards blood cells; or

(c) to keep the data to which the traceability system relates in accordance with the requirements of Article 15(4) of Regulation (EC) No 1394/2007.

Offence concerning data for advanced therapy medicinal products

88.—(1) A person who is, or immediately before its revocation or suspension was, the holder of an EU marketing authorisation relating to an advanced therapy medicinal product is guilty of an offence if the person fails to—

(a) keep the data referred to in Article 15(1) of Regulation (EC) No 1394/2007 in accordance with the requirements of Article 15(4) of that Regulation; or

(b) transfer the data referred to in Article 15(1) to the EMA in the event of that person's bankruptcy or liquidation in accordance with Article 15(5),

but this is subject to paragraph (2).

(2) Paragraph (1)(b) does not apply if—

(a) the person is bankrupt or in liquidation and has transferred the data to another person; or

(b) the period for which the person was required to keep the data in accordance with the requirements of Article 15(4) mentioned in paragraph (1)(a) has expired.

Offences relating to the Paediatric Regulation

Offences in connection with withdrawal of product from the market

89.—(1) This regulation applies to a person ("H") if—

(a) H is the holder of a UK marketing authorisation;

(b) H has benefited from one or more rewards or incentives under any of Articles 36, 37 and 38 of the Paediatric Regulation in relation to the product to which the authorisation relates, and

(c) all of the periods of protection provided pursuant to those Articles have expired in relation to H.

(2) H is guilty of an offence if H ceases to supply the product without previously in accordance with Article 35 of the Paediatric Regulation —

(a) transferring the UK marketing authorisation to another person who has declared an intention to continue to supply the product; or

(b) allowing such a person to use the pharmaceutical, pre-clinical and clinical documentation contained in the file on that product as provided for in regulation 56.

(3) H is guilty of an offence if H—

(a) ceases to supply the product; and

(b) does not in accordance with Article 35 of the Paediatric Regulation inform the EMA of H's intention to do so before the beginning of the period of six months ending immediately before the day on which H does so.

Failure to place on the market taking account of paediatric indication

90.—(1) A person ("P") is guilty of an offence if—

(a) P is the holder of a UK marketing authorisation;

(b) P obtains a paediatric indication in respect of the product to which the authorisation relates following completion of an agreed paediatric investigation plan;

(c) the product was placed on the market for other indications before P obtained that paediatric indication; and

(d) P fails to place the product on the market taking account of the paediatric indication in accordance with Article 33 of the Paediatric Regulation before the end of the period of two years beginning immediately after the day on which the paediatric indication is authorised.

(2) In this regulation "paediatric indication" means a term of the marketing authorisation enabling the product to which it relates to be used by or administered to persons under the age of 18 years.

Failure to notify results of third country clinical trials

91.—(1) This regulation applies to a person ("P") if—

(a) a decision by the EMA in respect of a paediatric investigation plan is addressed to P;

(b) the plan refers to clinical trials carried out in third countries ("third country clinical trials"); and

(c) P is established in the United Kingdom.

(2) P is guilty of an offence if P does not enter into the database referred to in Article 11 of the Clinical Trials Directive the details set out in that Article in relation to the third country clinical trials in accordance with Article 41(1) of the Paediatric Regulation within whichever is the later of—

(a) the period of one month beginning after the day on which the decision was received; or

(b) the period of one month beginning after the day on which the necessary permission to conduct the clinical trial was received from the competent authorities in the country where the clinical trial is to take place.

(3) P is guilty of an offence if P does not submit the results of those clinical trials to the EMA in accordance with Article 41(2) of the Paediatric Regulation within the period of—

(a) six months, if P is the holder of a marketing authorisation for the medicinal product concerned; or otherwise

(b) twelve months,

beginning with the day on which the last of those trials ended.

(4) Paragraph (3) does not apply, and regulation 93(3) shall apply, in the case of a clinical trial that forms part of a paediatric study to which regulation 93 applies.

Failure of sponsor of UK paediatric clinical trial to notify results of trial

92.—(1) This regulation applies to the sponsor ("S") of a paediatric clinical trial in the United Kingdom in respect of a medicinal product if—

(a) the product has a UK marketing authorisation but S is not the holder of the authorisation; or

(b) the product does not have a marketing authorisation.

(2) S is guilty of an offence if S does not submit the results of the clinical trial to the EMA in accordance with Article 41(2) of the Paediatric Regulation within the period of twelve months beginning with the day on which the trial ended.

Failure to notify results of paediatric study

93.—(1) This regulation applies to a person ("H") if—

(a) H is the holder of a UK marketing authorisation; and

(b) H sponsors a paediatric study in respect of the product to which the authorisation relates.

(2) H is guilty of an offence if H does not submit the results of the study to the licensing authority in accordance with Article 46(1) of the Paediatric Regulation within the period of six months beginning with the day on which the study ended.

(3) H is guilty of an offence if H does not submit the results of any clinical trial that forms part of that study to the EMA in accordance with Article 41(2) of the Paediatric Regulation within the period of six months beginning with the day on which the trial ended.

Failure to submit report to EMA

94. The holder of a marketing authorisation is guilty of an offence if the holder fails to submit an annual report to the EMA as required by Article 34(4) of the Paediatric Regulation.

General provisions relating to offences

Offences in connection with application

95. A person is guilty of an offence if, in the course of an application for the grant, renewal or variation of a marketing authorisation for a relevant medicinal product, the person—

(a) fails to provide the licensing authority with any information that is relevant to the evaluation of the safety, quality or efficacy of the product;

(b) provides to the licensing authority any information that is relevant to the evaluation of the safety, quality or efficacy of the product but that is false or misleading in a material particular;

(c) fails to provide the EMA with any information that is relevant to the evaluation of the safety, quality or efficacy of the product as required by paragraph (7) or (11) in the "Introduction and general principles" of Annex 1 to the 2001 Directive as applied by Article 6(1) of Regulation (EC) No 726/2004; or

(d) provides to the EMA any information of the kind described in sub-paragraph (c) that is false or misleading in a material particular.

Provision of false or misleading information

96.—(1) The holder of a marketing authorisation is guilty of an offence if the holder provides any information to which paragraph (2) applies that is relevant to the evaluation of the safety, quality or efficacy of a medicinal product but that is false or misleading in a material particular to—

(a) the licensing authority;

(b) the EMA; or

(c) the competent authorities of other EEA States.

(2) This paragraph applies to information about the product that is supplied pursuant to the obligations in—

(a) these Regulations; or

(b) Regulation (EC) No 726/2004.

(3) This regulation is without prejudice to the operation of regulation 95.

Breach of pharmacovigilance condition

97. The holder of a marketing authorisation is guilty of an offence if the holder fails to comply with a condition to which the marketing authorisation is subject by virtue of any of regulations 59 (conditions of UK marketing authorisation: general), 60 (conditions of UK marketing authorisation: exceptional circumstances) or 61 (conditions of UK marketing authorisation: new obligations post-authorisation).

General offence of breach of provision of this Part

98.—(1) A person is guilty of an offence if that person commits a breach of a provision in this Part.

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

(a) failure by the holder of a marketing authorisation to comply with any requirement or obligation in this Part:

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

(c) failure to comply with any requirement imposed on a person by the licensing authority pursuant to this Part.

(3) Paragraph (1) is without prejudice to any offence established by any other provision in this Part.

Penalties

99.—(1) A person guilty of an offence under this Part, other than a breach of regulation 79 (failure to provide information on marketing authorisations to EMA), 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 a breach of regulation 79 is liable—

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

(b) on conviction on indictment, to a fine.

Persons liable

100. If a breach of regulation 95 (offences in connection with application) 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.

Defences

101.—(1) Paragraph (2) applies if the holder of a marketing authorisation is charged with an offence under this Part in respect of anything that—

(a) has been manufactured or assembled to the holder's order by another person; and

(b) has been so manufactured or assembled as not to comply with the terms of the authorisation.

(2) It is a defence for the holder to prove that—

(a) the holder communicated the terms of the authorisation to the other person; and

(b) the holder did not know and could not by the exercise of reasonable care have known that those terms had not been complied with.

(3) It is a defence for a person charged with an offence consisting of a breach of regulations 73(3) or 78, or an offence under any of regulations 88 to 93, 95 and 96, to prove that the person took all reasonable precautions and exercised all due diligence to avoid commission of that offence.

(4) Where evidence is adduced that is sufficient to raise an issue with respect to the defence in paragraph (3), the court or jury must presume that the defence is satisfied unless the prosecution proves beyond reasonable doubt that it is not.