SCHEDULE 1

Regulation 3

Amendment of the Medicines (Products for Human Use) (Fees) Regulations 2016

Amendment of regulation 19 (capital fees for applications for variations of authorisations)

1. In regulation 19—

(a) in paragraph (1)(a), for paragraph (ii) substitute—

"(ii) 65C (variation of a UK marketing authorisation)"; and

(b) after paragraph (3) insert—

"(4) The reference in paragraph (1)(a)(ii) to an application under regulation 65C of the Human Medicines Regulations includes a reference to an application or notification submitted under paragraph 11(7) or 12(3) of Schedule 33A to the Human Medicines Regulations, or an application or notification which would have been submitted under those paragraphs but for its earlier submission in accordance with paragraph 13(1)(a) of that Schedule.".

Insertion of regulations 19A-19F (fees for plasma master files, vaccine antigen master files, post-authorisation safety studies, major safety reviews, periodic safety update reports and batch testing)

2. After regulation 19, insert—

"**Fees for certification of plasma master files**

19A.—(1) The fee payable by a person who submits a plasma master file to the licensing authority for scientific and technical evaluation in accordance with paragraph 1.1(c), second indent, of Part III of Annex I to the 2001 Directive, is £8,309.

(2) The fee payable by a person who submits a plasma master file to the licensing authority for re-certification in accordance with paragraph 1.1(c), third indent, of Part III of Annex I to the 2001 Directive is—

(a) £277, where there are no changes to the plasma master file other than an update to epidemiological data; or

(b) £734, in any other case.

Fee for certification of vaccine antigen master files

19B. The fee payable by a person who submits a vaccine antigen master file to the licensing authority for scientific and technical evaluation in accordance with paragraph 1.2(c), first indent, of Part III of Annex I to the 2001 Directive, is £8,309.

Fees for assessment of post-authorisation safety studies

19C.—(1) This regulation applies to post-authorisation safety studies initiated, managed or financed by the holder of a marketing authorisation in compliance with obligations imposed under regulation 59 or 61 of the Human Medicines Regulations.

(2) The fee payable by the holder of a marketing authorisation upon submission of the study protocol for a post-authorisation safety study in accordance with paragraph 29(1)(a) of Schedule 12A to the Human Medicines Regulations is £8,309.

(3) The fee payable by the holder of a marketing authorisation upon submission of the final study report for a post-authorisation safety study in accordance with paragraph 29(1)(b) of Schedule 12A to the Human Medicines Regulations is £8,309.

Fee for carrying out a major safety review

19D.—(1) Where the licensing authority conducts a major safety review of a marketing authorisation or traditional herbal registration, or a set of marketing authorisations or traditional herbal registrations, under regulation 196 of the Human Medicines Regulations, a fee is payable in accordance with Part 6A of Schedule 2.

(2) Unless paragraph (3) applies, the fee referred to in paragraph (1) is payable by the holder of the marketing authorisation or registration to which the review relates.

(3) Where the review relates to two or more authorisations or registrations the fee referred to in paragraph (1) is to be divided by the number of authorisations or registrations forming part of the review ("relevant authorisation or registration") and each holder of a relevant authorisation or registration must pay that reduced fee in respect of each relevant authorisation or registration it holds.

Fee for assessment of periodic safety update reports

19E.—(1) This regulation applies where—

(a) a periodic safety update report has been submitted to the licensing authority under regulation 191 or 192 of the Human Medicines Regulations; and

(b) that periodic safety update report relates to a medicinal product which has a UK reference date within the meaning of regulation 193 of the Human Medicines Regulations.

(2) Where this regulation applies, the fee payable by the holder of a marketing authorisation or traditional herbal registration to which the periodic safety update report relates is—

(a) £890, in the case where no other periodic safety update reports relating to medicinal products with the same UK reference date are submitted; and

(b) £445, in any other case.

Fee for testing of samples by the appropriate authority

19F.—(1) Where a sample from a batch of a medicinal product is submitted to the appropriate authority in accordance with a batch testing condition imposed under regulation 60A of the Human Medicines Regulations, the fee payable by the holder of the marketing authorisation to which the medicinal product relates is the fee prescribed in Part 6B of Schedule 2 in connection with that submission.

(2) The fee payable by an applicant for a certified copy of a certificate confirming that the appropriate authority is satisfied that the batch is in conformity with the approved specifications is £50.

(3) In this regulation, and in Part 6B of Schedule 2, "appropriate authority" and "batch testing condition" have the same meaning as in regulation 60A of the Human Medicines Regulations.

Time for payment of fees under regulations 19A to 19F

19G. All sums payable by way of fees under regulations 19A to 19F are payable on invoice.".

Amendment of regulation 23 (applications for multiple variations)

3.—(1) Regulation 23 is amended as follows.

(2) For paragraph (3)(b)(i) substitute—

"(i) have agreed should be subject to the procedure for grouping of variations within the meaning of paragraph 5(2)(c) of Schedule 10A to the Human Medicines Regulations; and".

(3) In paragraph (6), for "Article 5 of Commission Regulation (EC) No 1234/2008" substitute "paragraph 3 of Schedule 10A to the Human Medicines Regulations".

(4) In paragraph (7)—

(a) in the definition of "Major Variation (Type II) Group Application"—

(i) for sub-paragraph (b) substitute—

"(b) subject to sub-paragraph (c), the variations fall within the scope of paragraph 5(2)(b) or (c) of Schedule 10A to the Human Medicines Regulations;", and

(ii) for sub-paragraph (c)(i) substitute—

"(i) of a kind referred to in paragraph 5(3)(a) or (c) of Schedule 10A to the Human Medicines Regulations;";

(b) in the definition of "Major Variation (Type II) Complex Group Application"—

(i) for sub-paragraph (b) substitute—

"(b) subject to sub-paragraph (c), the variations fall within the scope of paragraphs 5(2)(b) or (c) of Schedule 10A to the Human Medicines Regulations;", and

(ii) for sub-paragraph (c)(i) substitute—

"(i) of a kind referred to in paragraph 5(3)(a) or (c) of Schedule 10A to the Human Medicines Regulations; or";

(c) in the definition of "Major Variation (Type II) Extended Complex Group Application"—

(i) for sub-paragraph (b) substitute—

"(b) subject to sub-paragraph (c), the variations fall within the scope of paragraph 5(2)(b) or (c) of Schedule 10A to the Human Medicines Regulations;", and

(ii) for sub-paragraph (c) substitute—

"(c) the variations do not include a variation of a kind referred to in paragraph 5(3)(a) of Schedule 10A to the Human Medicines Regulations; and";

(d) in the definition of "major variation of type II", for "Article 2(3) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations";

(e) in the definition of "Minor Variation (Type IB) Group Application"—

(i) for sub-paragraph (b) substitute—

"(b) subject to sub-paragraph (c), the variations fall within the scope of paragraph 5(2)(b) or (c) of Schedule 10A to the Human Medicines Regulations;", and

(ii) for sub-paragraph (c)(i) substitute—

"(i) a variation of a kind referred to in paragraph 5(3)(a) or (b) of Schedule 10A to the Human Medicines Regulations; or";

(f) in the definition of "minor variation of type IA", for "Article 2(2) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations";

(g) in the definition of "minor variation of type IB", for "Article 2(5) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations"; and

(h) omit the definition of "work sharing".

Insertion of regulation 27A (fee for renewals of a marketing authorisation)

4. After regulation 27, insert—

"**Fee for renewals of a marketing authorisation**

27A. Where an application is made to the licensing authority for the renewal of a marketing authorisation and the application for renewal—

(a) relates to a medicinal product which, at the time the marketing authorisation was granted, contained a new active ingredient; and

(b) is the first renewal in relation to that product,

the fee payable by the applicant is the fee prescribed in Part 6 of Schedule 2.".

Omission of Part 8 (Capital Fees for Regulatory Assistance Given by the United Kingdom Acting as Reference Member State Relating to the Assessment of Applications for the Renewal of Specified Marketing Authorisations)

5. Omit Part 8.

Amendment of Schedule 1 (general interpretation provisions)

6. In Schedule 1—

(a) in paragraph 1—

(i) in the definition of "medicinal product", for "includes any medicinal product for human use to which the 2001 Directive applies and" substitute "has the meaning given by regulation 2 of the Human Medicines Regulations and includes",

(ii) for the definition of "orphan medicinal product" substitute—

""orphan marketing authorisation" has the meaning given by regulation 8(1) of the Human Medicines Regulations;",

(iii) in the definition of "variation", for "Article 2(1) of Commission Regulation (EC) No 1234/2008" substitute "regulation 8(1) of the Human Medicines Regulations", and

(iv) at the appropriate places insert—

""Annex I to the 2001 Directive" has the meaning given by regulation 8(1) of the Human Medicines Regulations;";

""biological medicinal product" has the meaning given in paragraph 3.2.1.1. (b) of Part I of Annex I to the 2001 Directive;";

""the Committee for Medicinal Products for Human Use" means the committee established under Article 5(1) of Regulation (EC) No 726/2004;";

""the EMA" means the European Medicines Agency established by Regulation (EC) No 726/2004;"; and

(b) after paragraph 4 insert—

"**5.**—(1) For the purpose of these Regulations, a company is a medium company if, for the financial year before that in which the application is made, the total value of products it has sold or supplied for the financial year is not more than the amount for the time being specified in item 1 in section 465(3) of the Companies Act 2006(**1**) (qualification of company as medium) and the conditions in sub-paragraph (2) are met.

(2) The conditions for the purposes of sub-paragraph (1) are—

(a) the company's balance sheet total as defined in section 465(5) of the Companies Act 2006 is not more than the amount for the time being specified in item 2 in section 465(3) of that Act; or

(b) the average number of persons employed by the company in the financial year before that in which the application is made (determined on a weekly basis) does not exceed the number for the time being specified in item 3 in section 465(3) of that Act.

(3) In this paragraph "financial year" is to be construed in accordance with section 390 of the Companies Act 2006.".

Amendment of Schedule 2 (capital fees for applications for, and variations to, marketing authorisations, licences, registrations and certificates)

7.—(1) Schedule 2 is amended as follows.

(2) In paragraph 4(a), for "Article 2(4) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations".

(3) In paragraph 22—

(a) in sub-paragraph (1), for "Article 2(5) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations";

(b) in sub-paragraph (2)(f), for "Article 2(4) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations"; and

(c) in sub-paragraph (3), for "Article 2(2) of Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations".

(4) In paragraph 23—

(a) in sub-paragraph (a), for "paragraph 1 (changes to active substances) or paragraph 2 (changes to strength, pharmaceutical form and route of administration) of Annex I to Commission Regulation (EC) No 1234/2008 applies" substitute "sub-paragraph (a) (changes to active substances) or sub-paragraph (b) (changes to strength, pharmaceutical form and route of administration) of the definition of "extension of a UK marketing authorisation" in paragraph 1 of Schedule 10A to the Human Medicines Regulations apply";

(**1**) Section 465 was amended by S.I. 2015/980

(b) in sub-paragraph (b), for "Article 2(3) of Commission Regulation Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations"; and

(c) in sub-paragraph (c), for "Commission Regulation (EC) No 1234/2008" substitute "paragraph 1 of Schedule 10A to the Human Medicines Regulations".

(5) For the table in paragraph 24, substitute—

"**Fees for marketing authorisation applications**

Column 1 *Kind of application*	*Column 2* *Fee payable*
1. Major application	
(a) in respect of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use and in relation to which the applicant has provided such information relating to that opinion as has been requested by the licensing authority	£62,421
(b) in any other case	£92,753
2. Complex application	
(a) in respect of an application to which regulation 53 of the Human Medicines regulations applies, relating to a biological medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use and in relation to which the applicant has provided such information relating to that opinion as has been requested by the licensing authority	£17,330
(b) in any other case	£25,643
3. Standard application	£9,402
4. Simple application	£2,564
5. Parallel import licence applications	
(a) in respect of a simple parallel import licence	£1,792
(b) in respect of a standard parallel import licence	£6,663
(c) in respect of a complex parallel import licence	£18,180
6. Change of ownership application	£442".

(6) After paragraph 24, insert—

"**Fees where an application for a European Union marketing authorisation had been made before exit day**

24A.—(1) This paragraph applies where, before exit day—

(a) an application has been made to the EMA for a European Union marketing authorisation;

(b) day 120 has passed; and

(c) no final decision has been made by the European Commission in relation to the grant of an European Union marketing authorisation under Article 10 of Regulation (EC) No 726/2004.

(2) Where this paragraph applies and the applicant for the European Union marketing authorisation applies for a UK marketing authorisation in accordance with paragraph 31(2) of Schedule 33A to the Human Medicines Regulations, the fee payable under regulation 12(1) shall be waived.

(3) In this paragraph, "day 120" means the day during the assessment of an application for a European Union marketing authorisation on which the Committee for Medicinal Products for Human Use adopts the list of questions, as well as the overall conclusions and review of the scientific data, to be sent to the applicant.".

(7) In paragraph 27—

(a) in sub-paragraph (2), for paragraphs (a) to (c) substitute—

"(a) in respect of the first or only marketing authorisation applied for by that secondary applicant—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £17,330; or

(ii) in any other case, the amount payable in respect of a complex application under paragraph 24;

(b) in respect of each additional marketing authorisation applied for by that secondary applicant which relates to a medicinal product of the same dosage form—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24;

(c) in respect of the first additional marketing authorisation applied for by that secondary applicant relating to that medicinal product which is of a different dosage form—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £17,330; or

(ii) in any other case, the amount payable in respect of a complex application under paragraph 24;

(d) in respect of any other additional marketing authorisation applied for by that secondary applicant relating to that medicinal product which is of a different dosage form—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24."; and

(b) in sub-paragraph (3), for paragraph (a), substitute—

"(a) where the amount payable by the primary applicant is that in respect of a complex application, the fee payable under regulation 12(1)(a) by the secondary applicant is—

(i) in the case of an application relating to a biological medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24;".

(8) In paragraph 28—

(a) in sub-paragraph (2), for paragraphs (a) to (c) substitute—

"(a) in respect of each additional marketing authorisation applied for which relates to a medicinal product of a different dosage form with a different route of administration—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £17,330; or

(ii) in any other case, the amount payable in respect of a complex application under paragraph 24;

(b) in respect of each additional marketing authorisation applied for which relates to a medicinal product of a different dosage form but with the same route of administration—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24; and

(c) in respect of each additional marketing authorisation applied for which relates to a medicinal product of the same dosage form but of a different strength of active ingredient or different combination of active ingredients—

(i) in the case of an application relating to a medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24."; and

(b) in sub-paragraph (3), for paragraphs (b) and (c), substitute—

"(b) in respect of each additional marketing authorisation applied for which relates to a medicinal product of a different dosage form but with the same route of administration—

(i) in the case of an application relating to a biological medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24; and

(c) in respect of each additional marketing authorisation applied for which relates to a medicinal product of the same dosage form but of a different strength of active ingredient or different combination of active ingredients—

(i) in the case of an application relating to a biological medicinal product that has received an opinion favourable to the granting of a marketing authorisation from the Committee for Medicinal Products for Human Use, £6,350; or

(ii) in any other case, the amount payable in respect of a standard application under paragraph 24.".

(9) In paragraph 38—

(a) for sub-paragraph (4) substitute—

"(4) In sub-paragraph (1), the appropriate table is—

(a) in respect of a reclassification variation application, Table 3;

(b) in any other case, Table 2."; and

(b) omit table 1.

(10) In paragraph 39—

(a) in sub-paragraph (1), after "Subject to sub-paragraph (3)" insert "and paragraph 39A";

(b) in sub-paragraph (2), for "in respect of an orphan medicinal product", substitute "an orphan marketing authorisation"; and

(c) in sub-paragraph (3), for "an orphan medicinal product" substitute "a medicinal product which meets the orphan criteria listed in regulation 50G(2) of the Human Medicines Regulations".

(11) After paragraph 39, insert—

"**Variation of orphan marketing authorisations: small and medium companies**

39A.—(1) Subject to sub-paragraph (2), if an application to vary an orphan marketing authorisation is made by, or on behalf of, a small or a medium company within 12 months of the date of grant of the marketing authorisation, the fee payable for that variation application shall be waived.

(2) Sub-paragraph (1) does not apply to an application to authorise use of the medicinal product in a new therapeutic area which does not meet the orphan criteria listed in regulation 50G(2) of the Human Medicines Regulations.".

(12) After paragraph 40, insert—

"**Fees where an application for a variation or an extension of a European Union marketing authorisation had been made before exit day**

40A.—(1) Paragraph (2) applies where, before exit day—

(a) an application for a variation to which paragraph 11(7) of Schedule 33A to the Human Medicines Regulations applies, has been made to the EMA; and

(b) the Committee for Medicinal Products for Human Use has adopted a request for supplementary information to be sent to the applicant, or, in the case of an extension, day 120 has passed.

(2) Where this paragraph applies and the holder of a converted EU marketing authorisation submits the application to the licensing authority in order to have the variation made to the converted EU marketing authorisation, the fee payable under regulation 19(1) shall be waived.

(3) In this paragraph—

"day 120" means the day during the assessment of an extension on which the Committee for Medicinal Products for Human Use adopts the list of questions, as well as the overall conclusions and review of the scientific data, to be sent to the applicant;

"converted EU marketing authorisation" has the meaning given in paragraph 6(1) and (2) of Schedule 33A to the Human Medicines Regulations; and

"extension" has the meaning given in paragraph 1 of Schedule 10A to the Human Medicines Regulations.".

(13) For Part 6 substitute—

"PART 6

Capital Fee for the Renewal of a Marketing Authorisation

Renewal of a marketing authorisation

56. Unless paragraph 57 applies, the fee payable under regulation 27A in connection with an application for the renewal of a United Kingdom marketing authorisation is £9,682.

Renewal of multiple marketing authorisations

57.—(1) This sub-paragraph applies if more than one application falling within regulation 27A is made by the same applicant at the same time, each of which relates to medicinal products which have the same active ingredient or combination of ingredients, dosage form and therapeutic indications, and the marketing authorisations for those products have the same date for renewal.

(2) The fee payable under regulation 27A for applications to which sub-paragraph (1) applies is—

(a) £9,682 for the first application considered by the licensing authority; and

(b) £747 for each other application.

PART 6A

Capital Fee for Conducting a Major Safety Review

57A. The fee payable under regulation 19D(1) in connection with the carrying out of a major safety review is—

(a) £51,286, where one or two active ingredients, or combinations of active ingredients, are included in the assessment;

(b) £59,595, where three active ingredients, or combinations of active ingredients, are included in the assessment;

(c) £67,904, where four active ingredients, or combinations of active ingredients, are included in the assessment; or

(d) £76,213, where five or more active ingredients, or combinations of active ingredients, are included in the assessment.

PART 6B

Capital Fee for Testing of Samples by the Appropriate Authority

57B.—(1) Unless sub-paragraph (2) applies, the fee payable under regulation 19F(1) in connection with the submission of a sample of a batch of a medicinal product of a kind described in column 1 of the following table is the fee specified in the corresponding entry in column 2 of that table.

(2) This sub-paragraph applies where—

(a) the holder of the marketing authorisation submits, with a sample of a batch of medicinal product, a certificate issued by a laboratory in a designated country for batch testing and certification of biological medicinal products that relates to the sample of the batch submitted; and

(b) on the basis of the documentation submitted with the sample, the appropriate authority considers that it is only necessary to carry out a paper based assessment of the sample.

(3) Where sub-paragraph (2) applies, the fee payable under regulation 19F(1) in connection with the submission of a sample of a batch of medicinal product of a kind described in column 1 of the following table is the fee specified in the corresponding entry in column 3 of that table.

(4) Where a product falls within more than one of the Bands referred to in the following table, the product is to be treated as if it only falls within the Band which attracts the highest fee.

Fees for testing of samples

Column 1 *Product Type*	*Column 2* *Fee payable where the licensing authority carries out a full assessment*	*Column 3* *Fee payable where the licensing authority carries out a paper-based assessment*
1. Plasma pools which require—		
(a) three or fewer tests	£180	£90
(b) four or five tests	£215	£90
(c) six or more tests	£230	£90
2. Band A	£1,660	£305
3. Band B	£1,910	£305
4. Band C	£2,340	£305
5. Band D	£3,690	£677
6. Band E	£6,410	£677
7. Band F	£10,350	£677

(5) In this paragraph—

"Band A" means a single component product, other than Botulinum toxin, requiring five or fewer in vitro tests;

"Band B" means Factor VIII, Factor IX or intravenous Immunoglobulin;

"Band C" means a multi-component product, or Botulinum toxin, requiring five or fewer in vitro tests;

"Band D" means a product requiring six to nine in vitro tests;

"Band E" means a product requiring—

(a) ten or more in vitro tests, or

(b) one or more in vivo tests;

"Band F" means a product—

(a) which requires one or more tests that must be carried out under containment measures applicable to hazard Group 3 or 4 biological agents under the Control of Substances Hazardous to Health Regulations 2002(**2**); or

(b) requires the use of human cells or tissues as part of its testing;

"Multi-component product" means a product containing two or more analytes that require testing; and

"Single component product" means a product containing a single analyte that requires testing."

Amendment of Schedule 4 (periodic fees for licences)

8. In Schedule 4, in paragraph 1, in the definition of "limited use drug" for "which is in respect of an orphan medicinal product" substitute "in respect of which an orphan marketing authorisation has been granted".

Amendment of Schedule 7 (waiver, reduction or refund of capital fees)

9. In Schedule 7, after paragraph 7, insert—

"**Orphan marketing authorisation**

7A. Where the licensing authority grants an orphan marketing authorisation, the following percentage of the fee otherwise payable under regulation 12(1)(a) in connection with the application for that authorisation shall be refunded or, if it has not yet been paid, shall be waived—

(a) in the case of an application made by or on behalf of a small or medium company, 100%;

(b) in the case of a major application that is not made by or on behalf of a small or medium company but to which paragraph 6 of Part II of Annex 1 to the 2001 Directive applies, 50%; or

(c) in any other case, 10%.".

Amendment of Schedule 8 (Adjustment, reduction or refund of periodic fees)

10.—(1) Schedule 8 is amended as follows.

(2) In the heading, after "Adjustment", insert ", waiver".

(3) After paragraph 2, insert—

(**2**) S.I. 2002/2677

"**Waiver or refund: converted EU marketing authorisations**

2A.—(1) Where the licensing authority revokes a converted EU marketing authorisation in accordance with paragraph 6(3) of Schedule 33A to the Human Medicines Regulations, the periodic fee payable under regulation 38(1) in relation to that authorisation shall be refunded, or if it has not yet been paid, shall be waived.

(2) In this paragraph, "converted EU marketing authorisation" has the meaning given in paragraph 6(1) and (2) of Schedule 33A to the 2012 Regulations."

Savings

11.—(1) The provisions of the Medicines (Products for Human Use) (Fees) Regulations 2016 ("the 2016 Regulations") omitted, substituted or amended by this Schedule shall continue to apply as if they had not been omitted, substituted or amended in relation to—

(a) capital fees payable under the 2016 Regulations in respect of any application or inspection made before the date on which these Regulations come into force; and

(b) any periodic fee payable under the 2016 Regulations in relation to the fee period during which these Regulations come into force or in relation to a fee period ending before the date on which these Regulations come into force.

(2) The omissions, substitutions and amendments shall not affect any proceedings under the 2016 Regulations for the recovery of any fees due as debts to the Crown and for the purposes of those proceedings, the provisions omitted, substituted or amended by this Schedule shall continue to apply as if they had not been omitted, substituted or amended.

SCHEDULE 2 Regulation 11

Insertion of new Schedule 8B (modifications of Annex I to the 2001 Directive)

1. After Schedule 8A to the Human Medicines Regulations 2012, insert—

"SCHEDULE 8B Regulation 8(1)

Modifications of Annex I to the 2001 Directive

Provision of Annex I	*Modification subject to which that provision is to be read*
Paragraph (1) of the Introduction and general principles	The reference to "Articles 8 and 10(1)" is to be read as a reference to regulation 50 of the Human Medicines Regulations 2012.
Paragraphs (1) and (2) of the Introduction and general principles	If the licensing authority has published guidelines under regulation 50(5B)(a) of the Human Medicines Regulations 2012, the reference to "the rules governing medicinal products in the European Community, Volume 2B, Notice to applicants, medicinal products for human use, presentation and content of the dossier, Common Technical Document" is to be read as a reference to that guidance.

Provision of Annex I	*Modification subject to which that provision is to be read*
Paragraph (4) of the Introduction and general principles	If the licensing authority has published guidelines under regulation 50(5B)(b) of the Human Medicines Regulations 2012, the reference to "the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and the European Medicines Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of the rules governing medicinal products in the European Community" is to be read as a reference to those guidelines.
Paragraph (6) of the Introduction and general principles	The reference to "the requirements of Commission Directive 91/356/EEC laying down the principles of and guidelines of Good Manufacturing Practice for medicinal products for human use" is to be read as a reference to the Good Manufacturing Practice Directive, as defined in regulation 8(1) of the Human Medicines Regulations 2012.
Paragraph (6) of the Introduction and general principles	If the licensing authority has published principles and guidelines under regulation C17(1) of the Human Medicines Regulations 2012, the reference to "the principles and guidelines on GMP published by the Commission in the rules governing medicinal products in the European Community, Volume 4" is to be read as a reference to those principles and guidelines.
Paragraph (8) of the Introduction and general principles	References to "the European Community" are to be read as references to the United Kingdom.
Paragraph (8) of the Introduction and general principles	The references to "Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" are to be read as references to the Medicinal Products for Human Use (Clinical Trials) Regulations 2004(**3**).
Paragraph (9) of the Introduction and general principles	The reference to "Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the

(**3**) S.I. 2004/1157.

Provision of Annex I	*Modification subject to which that provision is to be read*
	application of the principles of good laboratory practice and the verification of their application for tests in chemical substances and 88/320/EEC on the inspection and verification of good laboratory practice" is to be read as a reference to the Good Laboratory Practice Regulations 1999(**4**).
Paragraph (10) of the Introduction and general principles	The reference to "Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes" is to be read as a reference to the Animals (Scientific Procedures) Act 1986(**5**).
Paragraph (11) of the Introduction and general principles	The paragraph is to be read as follows: "In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmacovigilance information shall be submitted to the licensing authority. After a marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the licensing authority in accordance with the requirements of Schedule 10A to the Human Medicines Regulations 2012, as well as the requirements of Schedule 12A to those Regulations."
Part I, paragraph 1.2, fourth paragraph	This paragraph is to be read as follows: "Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in regulation 17 of the Human Medicines Regulations 2012."
Part I, paragraph 1.3.1	The reference to "Article 11" is to be read as a reference to Part 2 of Schedule 8 to the Human Medicines Regulations 2012.
Part I, paragraph 1.3.2	The reference to "Title V" is to be read as a reference to Part I3 of the Human Medicines Regulations 2012, and the references to Articles 63 and 59 are to be read as references to regulations 260 and 266 of the Human Medicines Regulations 2012.
Part I, paragraph 1.3.4	This paragraph is to be read as omitted.

(**4**) S.I. 1999/3106.
(**5**) 1986 c. 14, as amended by S.I. 2012/3039.

Provision of Annex I	*Modification subject to which that provision is to be read*
Part I, paragraph 1.4	The reference to "Article 12.2" is to be read as a reference to paragraph 11 of Schedule 8 to the Human Medicines Regulations 2012.
Part I, paragraph 2, first paragraph	The reference to "Article 12" is to be read as a reference to paragraph 11 of Schedule 8 to the Human Medicines Regulations 2012.
Part I, paragraph 3.2(5), first paragraph	The reference to a "Member State" is to be read as including the United Kingdom.
Part I, paragraph 3.2(5), second paragraph	The references to "the national pharmacopoeia of a Member State" are to be read as including references to the British Pharmacopoeia.
Part I, paragraph 3.2(6)	The reference to "the pharmacopoeia of a Member State" is to be read as including a reference to the British Pharmacopoeia.
Part I, paragraph 3.2(12)	The words "which is required by Community legislation" are to be read as omitted.
Part I, paragraph 3.2.1.2	If the licensing authority has published guidelines under regulation 50(5B)(c) of the Human Medicines Regulations 2012, the reference to "guidelines published by the Agency" is to be read as a reference to those guidelines.
Part I, paragraph 3.2.2.1, second paragraph	The reference to "Article 8(3)(c)" is to be read as a reference to paragraph 3 of Schedule 8 to the Human Medicines Regulations 2012.
Part I, paragraph 3.2.2.1, second paragraph, first indent	The reference to "the national pharmacopoeia of one of the Member States" is to be read as including the British Pharmacopoeia.
Part I, paragraph 3.2.2.1, fifth paragraph	The reference to "any Member State" is to be read as a reference to the United Kingdom and the reference to "the Member States" is to be read as a reference to the United Kingdom.
Part I, paragraph 3.2.2.3(a)	The reference to "Article 8(3)(d)" is to be read as a reference to paragraph 5 of Schedule 8 to the Human Medicines Regulations 2012.
Part I, paragraph 4.2.2, fifth paragraph	The reference to "this Directive" is to be read as a reference to the Human Medicines Regulations 2012.
Part I, paragraph 5.2(a)	The reference to "the clinical particulars provided pursuant to Articles 8(3)(i) and 10(1)" is to be read as a reference to those particulars provided pursuant to paragraph 10 of Schedule 8 to, and regulations 51 to 56 of, the Human Medicines Regulations 2012.

Provision of Annex I	*Modification subject to which that provision is to be read*
Part I, paragraph 5.2(c)	The references to "the European Community" are to be read as references to the United Kingdom.
Part I, paragraph 5.2(c), fifth paragraph	The reference to "Directive 2001/20/EC and implementing detail guidelines" is to be read as a reference to the Medicinal Products for Human Use (Clinical Trials) Regulations 2004(**6**).
Part I, paragraph 5.2.1, second paragraph	The reference to "Article 10(1)(a)" is to be read as a reference to regulation 51 of the Human Medicines Regulations 2012.
Part II, paragraph 1, first paragraph	The reference to "Article 10(1)(a)(ii)" is to be read as a reference to regulation 54 of the Human Medicines Regulations 2012.
Part II, paragraph 2(a)	The reference to "Article 10(1)(a)(i)" is to be read as a reference to regulation 56 of the Human Medicines Regulations 2012.
Part II, paragraph 2(b)	The reference to "Article 10(1)(a)(ii)" is to be read as a reference to regulation 51 of the Human Medicines Regulations 2012.
Part II, paragraph 4, first paragraph	The first sentence is to be read as omitted and the words "in accordance with regulation 53 of the Human Medicines Regulations 2012" are to be read as added at the end of the second sentence.
Part II, paragraph 5, first paragraph	The reference to "Article 10(1)(b)" is to be read as a reference to regulation 55 of the Human Medicines Regulations 2012.
Part II, paragraph 6, first paragraph	The reference to "Article 22" is to be read as a reference to regulation 60 of the Human Medicines Regulations 2012.
Part III, paragraph 1.1(a), first indent	The reference to "Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or blood plasma" is to be read as a reference to the Medical Devices Regulations 2002(**7**).
Part III, paragraph 1.1(a), third indent	The reference to "the Agency or the competent authority" is to be read as a reference to the licensing authority.

(**6**) S.I. 2004/1157.
(**7**) S.I. 2002/618.

Provision of Annex I	*Modification subject to which that provision is to be read*
Part III, paragraph 1.1(a), fourth indent	This indent is to be read as omitted.
Part III, paragraph 1.1(b)	The reference to "Article 109, as amended by Directive 2002/98/EC" is to be read as a reference to the Blood Safety and Quality Regulations 2005(**8**).
Part III, paragraph 1.1(b)(3), second paragraph	The reference to "medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" is to be read as a reference to investigational medicinal products.
Part III, paragraph 1.1.(c), second indent	This indent is to be read as follows: "The Plasma Master File is subject to a scientific and technical evaluation by the licensing authority."
Part III, paragraph 1.1(c), fourth indent	This indent is to be read as follows: "Changes subsequently introduced to the terms of a Plasma Master File must follow the variation procedure in Schedule 10A to the Human Medicines Regulations 2012."
Part III, paragraph 1.1(c), final indent	This indent is to be read as omitted.
Part III, paragraph 1.2(c), first indent	The references to "a competent authority" and to "the Agency" are to be read as references to the licensing authority and the final two sentences are to be read as omitted.
Part III, paragraph 1.2(c), second indent	The reference to "the Community" is to be read as a reference to the United Kingdom.
Part III, paragraph 1.2(c), third indent	This indent is to be read as follows: "Changes in the content of a Vaccine Antigen Master File must follow the variation procedure in Schedule 10A to the Human Medicines Regulations 2012."
Part III, paragraph 1.2(c), fourth indent	This indent is to be read as omitted.
Part III, paragraph 1.2(c), fifth indent	This indent is to be read as omitted.
Part III, paragraph 2.1	The reference to "applications based on Articles 6(2) and 9" is to be read as a reference to applications in relation to radionuclide generators, radionuclide kits, radionuclide precursors and radiopharmaceuticals.

(**8**) S.I. 2005/50.

Provision of Annex I	*Modification subject to which that provision is to be read*
Part III, paragraph 2.2, fourth paragraph	The reference to "Council Directives 87/18/EEC and 88/320/EEC" is to be read as a reference to the Good Laboratory Practice Regulations 1999(**9**).
Part III, paragraph 3, second paragraph	The reference to "Article 15" is to be read as a reference to regulation 103 of the Human Medicines Regulations 2012, the reference to "Article 14(1)" is to be read as a reference to regulation 102 of the Human Medicines Regulations 2012 and the words "referred to in Article 16(1)" are to be read as "which are not registerable homoeopathic medicinal products".
Part III, paragraph 3(a)	The reference to "an official pharmacopoeia of a Member State" is to be read as including the British Pharmacopoeia and any pharmacopoeia used officially in a country that is included in a list published by the licensing authority for that purpose, and the reference to "the traditional names used in each Member State" is to be read as including the traditional name used in the United Kingdom.
Part III, paragraph 3(b), final paragraph	The reference to "an official pharmacopoeia of a Member State" is to be read as including the British Pharmacopoeia.
Part III, paragraph 3, penultimate paragraph	The reference to "Article 14(1)" is to be read as a reference to regulation 102 of the Human Medicines Regulations 2012.
Part III, paragraph 5, first indent	The reference to "an orphan medicinal product in the meaning of Regulation (EC) No 141/2000" is to be read as a reference to a medicinal product to which the orphan criteria are claimed to apply.
Part III, paragraph 5, second indent	The reference to "Article 10(1)(a)(ii)" is to be read as a reference to regulation 54 of the Human Medicines Regulations 2012 and the reference to "Article 5" is to be read as a reference to regulation 167 of the Human Medicines Regulations 2012.
Part IV, paragraph 1, first paragraph	The reference to "point (a) of Article 2(1) of Regulation (EC) No 1394/2007" is to be read as a reference to regulation 2A of the Human Medicines Regulations 2012.
Part IV, paragraph 2	This paragraph is to be read as omitted.

(**9**) S.I. 1999/3106.

Provision of Annex I	*Modification subject to which that provision is to be read*
Part IV, paragraph 3.1, second paragraph	The reference to "Directive 2004/23/EC" is to be read as a reference to the Human Fertilisation and Embryology Act 1990(**10**) and the Human Tissue (Quality and Safety for Human Application) Regulations 2007(**11**) and the reference to "Directive 2002/98/EC" is to be read as a reference to the Blood Safety and Quality Regulations 2005(**12**).
Part IV, paragraph 3.3.2.1(a)	The reference to "Directive 2004/23/EC" is to be read as a reference to the Human Fertilisation and Embryology Act 1990 and the Human Tissue (Quality and Safety for Human Application) Regulations 2007.
Part IV, paragraph 3.4.1, heading	The reference to "devices as referred to in Article 7 of Regulation (EC) No 1394/2007" is to be read as a reference to medical devices, bio-materials, scaffolds or matrices.
Part IV, paragraph 3.4.2, heading	The reference to "Article 2(1)(d) of Regulation (EC) No 1394/2007" is to be read as a reference to regulation 2A(10) of the Human Medicines Regulations 2012.
Part IV, paragraph 3.4.2(c)	The reference to "Commission Directive 2003/32/EC" is to be read as a reference to the Medical Devices Regulations 2002.
Part IV, paragraph 3.4.2(d)	The reference to "Directive 93/42/EEC or Directive 90/385/EEC" is to be read as a reference to the Medical Devices Regulations 2002(**13**).
Part IV, paragraph 3.4.2, final paragraph	The first sentence is to be read as follows: "The applicant shall make available on request of the licensing authority any information related to the assessment by the notified body which has carried out the assessment referred to in point (d) of this section."".

SCHEDULE 3

Regulation 12

Insertion of new Schedule 2A (modifications of Commission Directive 2003/94/EC)

1. After Schedule 2 to the Human Medicines Regulations 2012, insert—

(**10**) 1990 c. 37.
(**11**) S.I. 2007/1523.
(**12**) S.I. 2005/50.
(**13**) S.I. 2002/618.

"SCHEDULE 2A Regulations 8(1) and B17(3)

Modifications of Commission Directive 2003/94/EC

Provision of Commission Directive 2003/94/EC	*Modification subject to which that provision is to be read*
Article 1 (scope)	The reference to— (a) "Article 40 of Directive 2001/83/EC" is to be read as a reference to "regulation 17 of the Human Medicines Regulations 2012"; and (b) "Article 13 of Directive 2001/20/EC" is to be read as a reference to "regulation 36 of the Medicines for Human Use (Clinical Trials) Regulations 2004".
Article 2 (definitions)	In the definition of— (a) "medicinal product", the reference to "Article 1(2) of Directive 2001/83/EC" is to be read as a reference to "regulation 2 of the Human Medicines Regulations 2012"; (b) "investigational medicinal product", the reference to "Article 2(d) of Directive 2001/20/EC" is to be read as a reference to "regulation 2(1) of the Medicines for Human Use (Clinical Trials) Regulations 2004"; (c) "manufacturer" the reference to "Article 40(1) and (3) of Directive 2001/83/EC or the authorisation referred to in Article 13(1) of Directive 2001/20/EC" is to be read as a reference to "regulation 17(1) of the Human Medicines Regulations 2012 or the authorisation referred to in regulation 36(1) of the Medicines for Human Use (Clinical Trials) Regulations 2004"; (d) "qualified person" the reference to "Article 48 of Directive 2001/83/EC or in Article 13(2) of Directive 2001/20/EC" is to be read as a reference to "regulation 41 of the Human Medicines Regulations 2012 or regulation 43 of the Medicines for Human Use (Clinical Trials) Regulations 2004".
Article 3(1) (inspections)	The reference to— (a) "for Article 111(1) of Directive 2001/83/EC" is to be read as a reference to "Part 16

Provision of Commission Directive 2003/94/EC	*Modification subject to which that provision is to be read*
	of the Human Medicines Regulations 2012 (enforcement)"; (b) "Article 15(1) of Directive 2001/20/EC" is to be read as a reference to "Part 8 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (enforcement)"; (c) "the Member States", is to be read as a reference to "the licensing authority"; (d) "Member States shall" is to be read as a reference to "The licensing authority may"; (e) "published by the Commission, of Community procedures on inspections and exchanges of information" is to be read as if after it there were inserted "or any guidance published by the licensing authority to replace that Commission guidance".
Article 3(2) (inspections)	The reference to— (a) "competent authorities" is to be read as a reference to "licensing authority"; (b) "the second paragraph of Article 47 of Directive 2001/83/EC" to the end is to be read as a reference to "regulation C17(1)(a) of the Human Medicines Regulations 2012, or which applies by virtue of regulation C17(2) of those Regulations".
Article 4(2) (conformity with good manufacturing practice)	The reference to— (a) "third countries" is to be read as a reference to "country other than the United Kingdom"; (b) "Community" is to be read as a reference to "licensing authority".
Article 5 (compliance with marketing authorisation)	The reference to— (a) "Article 9(2) of Directive 2001/20/EC" in both places it appears is to be read as a reference to "regulation 17 of the Medicines for Human Use (Clinical Trials) Regulations 2004";

Provision of Commission Directive 2003/94/EC	*Modification subject to which that provision is to be read*
	(b) "competent authorities" in both places it appears is to be read as a reference to "licensing authority".
Article 9 (documentation)	The reference in— (a) paragraph (1) to "Article 51(3) of Directive 2001/83/EC" is to be read as a reference to "paragraph 15(1) of Schedule 7 to the Human Medicines Regulations 2012"; (b) paragraph (2) to "competent authorities" is to be read as a reference to "licensing authority".
Article 11 (quality control)	The reference in paragraph (2)— (a) to "point (b) of Article 20 of Directive 2001/83/EC" is to be read as a reference to "paragraph 3 or 17 of Schedule 4 to the Human Medicines Regulations 2012"; (b) to "Article 9(2) of Directive 2001/20/EC" is to be read as a reference to "regulation 17 of the Medicines for Human Use (Clinical Trials) Regulations 2004"; The reference in paragraph (4)— (a) to "Member State" is to be read as a reference to "United Kingdom"; (b) to "competent authority" is to be read as a reference to "licensing authority";
Article 12(4) (work contracted out)	The reference to— (a) "competent authorities" is to be read as a reference to "licensing authority"; (b) "for Article 111 of Directive 2001/83/EC and Article 15(1) of Directive 2001/20/EC" is to be read as a reference to "Part 16 of the Human Medicines Regulations 2012 or Part 8 of the Medicines for Human Use (Clinical Trials) Regulations 2004".
Article 13 (complaints, product recall and emergency unblinding)	The reference to "Article 123 of Directive 2001/83/EC" is to be read as a reference to "Part 5 of the Human Medicines Regulations 2012"."

SCHEDULE 4 Regulation 54

Insertion of new Schedule 9A

1. After Schedule 9, insert—

"SCHEDULE 9A Regulation 50G(4)

Meaning of terms used in the orphan criteria and in regulation 58D

Prevalence of a condition in the United Kingdom

1.—(1) The following provisions apply for the purposes of establishing, pursuant to regulation 50G(2)(a) and (b)(i), that a medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the United Kingdom.

(2) The material provided pursuant to regulation 50G(3) must include—

(a) material which demonstrates that the disease or condition for which the medicinal product would be authorised affects not more than five in 10,000 persons in the United Kingdom at the time at which the application for an orphan marketing authorisation is submitted, where this is available;

(b) details of the condition intended to be treated and a justification of the life-threatening or chronically debilitating nature of the condition, supported by scientific or medical references; and

(c) copies of, or references to, relevant scientific literature, as well as copies of information from relevant databases in the United Kingdom, where available.

(3) If there are no databases as referred to in paragraph (2)(c), information from relevant databases in other countries may be supplied, provided appropriate extrapolations are made.

Potential for return on investment

2.—(1) The following provisions apply for the purposes of establishing, pursuant to regulation 50G(2)(a) and (b)(ii), that a medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition in the United Kingdom and that the medicinal product is unlikely, when marketed, to generate sufficient financial return to justify the necessary investment.

(2) The material provided pursuant to regulation 50G(3) must include—

(a) details of the condition intended to be treated and a justification of the life-threatening or chronically debilitating nature of the condition, supported by scientific or medical references;

(b) details of the costs incurred in connection with the development of the medicinal product;

(c) details of any grants, tax incentives or other cost recovery provisions received in the United Kingdom or any other country in relation to the development of the medicinal product;

(d) where the medicinal product is already authorised in the United Kingdom for any indication, or where the product is under investigation for one or more other indications, an explanation of, and justification for, the method that is used to apportion the development costs among the various indications;

(e) a statement of and justification for all development costs that the applicant expects to incur after the submission of the application for a UK marketing authorisation;

(f) a statement of and justification for all production and marketing costs that the applicant has incurred in the past and expects to incur in the first ten years that the medicinal product is authorised;

(g) an estimate of and justification for the expected revenues from sales of the medicinal product in the United Kingdom and elsewhere during the first ten years that the medicinal product is authorised; and

(h) information on the prevalence and incidence in the United Kingdom of the condition for which the medicinal product would be authorised at the time at which the application for an orphan marketing authorisation application is submitted.

(3) The information concerning costs and revenue referred to in sub-paragraph (2) must be determined in accordance with generally accepted accounting principles and must be certified by a person who is a member of a body of accountants which is established in the United Kingdom and which is approved by the licensing authority for the purposes of this paragraph.

Existence of other methods of diagnosis, prevention or treatment

3.—(1) The following provisions apply for the purposes of establishing, pursuant to regulation 50G(2)(c), that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the United Kingdom, or if such method exists, that the medicinal product will be of significant benefit to those affected by the condition.

(2) The material provided pursuant to regulation 50G(3) must include—

(a) details of any existing methods of diagnosis, prevention or treatment of the condition in question that have been authorised in the United Kingdom, making reference to scientific or medical literature or other relevant information, including information relating to authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the United Kingdom; and

(b) a justification as to why either—

(i) the methods referred to in paragraph (a) are not considered satisfactory; or

(ii) the medicinal product for which an orphan marketing authorisation is sought will be of significant benefit to those affected by the condition.

(3) In this paragraph, "significant benefit" means a clinically relevant advantage or a major contribution to patient care.

Increased safety or effectiveness and clinical superiority

4.—(1) The following provisions apply for the purposes of establishing, pursuant to regulation 58D(6)(c), that a second medicinal product is similar to a medicinal product to which an orphan marketing authorisation relates or is safer or more effective than, or clinically superior to, that product.

(2) The following definitions apply for the purposes of this paragraph—

"clinically superior", in relation to a medicinal product, means that it is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways—

(a) greater efficacy;

(b) greater safety in a substantial portion of the target population, as evidenced where appropriate through comparative clinical trials; or

(c) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care;

"similar active substance" means an identical active substance, or an active substance with the same principal molecular structural features, but not necessarily all of the same molecular structural features, and which acts via the same mechanism, however, in the case of advanced therapy medicinal products, for which the principal molecular structural features cannot be fully defined, the similarity between two active substances is to be assessed on the basis of the biological and functional characteristics;

"similar medicinal product" means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication.

(3) For the purposes of the definition of "clinically superior" in relation to a medicinal product which shows that superiority by means of greater efficacy, this is to be assessed by the effect on a clinically meaningful endpoint in adequate and well controlled clinical trials, representing the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products.

(4) The clinical trials referred to in paragraph (3) should be direct comparative clinical trials, unless comparisons based on other endpoints, including surrogate endpoints, can be justified.

(5) Paragraphs 5 to 8 make further provision about the definition of "similar active substance" in relation to certain types of product.

5.—(1) This paragraph applies for the purposes of the definition of "similar active substance" in relation to chemical medicinal products.

(2) The principal molecular structural features are the relevant structural components of an active substance, which may be the whole or part of the molecule.

(3) Whether the principal molecular structural features are the same between two or more molecules will be identified by comparison of their structures.

(4) Isomers, mixtures of isomers, complexes, esters, ethers, salts and derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue, are to be considered similar.

(5) Synthetic polynucleotide substances, single or double stranded, consisting of two or more distinct nucleotides where—

(a) the difference in the nucleotide sequence of the purine and pyrimidine bases or their derivatives is not major, are to be considered similar, therefore for antisense or interfering nucleotide substances, addition, substitution or deletion of a nucleotide not significantly affecting the kinetics of hybridisation to the target are usually to be considered similar; and

(b) the difference in structure related to modifications of the ribose or deoxyribose backbone sugars or to the replacement of the backbone sugars by synthetic analogues usually result in substances being considered similar, and for antisense or interfering nucleotide substances, changes in the ribose or deoxyribose backbone sugars not significantly affecting the kinetics of hybridisation to the target are usually to be considered similar.

6.—(1) This paragraph applies for the purposes of the definition of "similar active substance" in relation to biological medicinal products other than advanced therapy medicinal products.

(2) The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics of that substance.

(3) The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element significantly contributing to the functional characteristics of the active substance.

(4) An additional structural element as described in paragraph (3) may be conjugated, fused or linked by other means to the therapeutic moiety or may be an extension of the therapeutic moiety protein backbone by additional amino acids.

(5) Substances with structural elements for which similar methods of modification or conjugation technology are used usually result in similar substances.

(6) Biological active substances which differ from the original biological substance only with respect to minor changes in the molecular structure are to be considered similar.

(7) In relation to proteinaceous substances—

(a) if the difference in structure between them is due to post-translational events, such as different glycosylation patterns, substances are usually to be considered similar; however, exceptionally some post-translational modifications may result in a non-similar substance if there is significant effect on the functional characteristics of the substance;

(b) if the difference in the amino acid sequence is not major, substances are usually to be considered similar; therefore two pharmacologically related protein substances of the same group, for example, having differences related to N-terminal methionine, naturally extracted as opposed to recombinant nucleic acid-derived proteins or other minor variants, are usually to be considered similar; however, the addition of a structural element may result in substances not being considered similar if this significantly affects the functional characteristics of the substance;

(c) monoclonal antibodies binding to the same target epitope are usually to be considered similar; however, two monocloncal antibody conjugates or fusion proteins may be considered not to be similar if either the Complementary Determining Region sequences of the antibody or the additional structural element of the conjugated monoclonal antibody is different.

(8) In relation to polysaccharide substances—

(a) if the substances have identical saccharide repeating units, even if the number of units varies, the substances are usually to be considered similar; and

(b) a conjugated polysaccharide vaccine compared to a non-conjugated polysaccharide vaccine containing the same antigen is considered not to be similar.

7.—(1) This paragraph applies for the purposes of the definition of "similar active substance" in relation to advanced therapy medicinal products.

(2) In relation to cell-based advanced therapy medicinal products, these are not to be considered similar if—

(a) there are differences in starting materials or the final composition of the product which have a significant impact on the biological characteristics or biological activity relevant for the intended therapeutic effect or safety attributes of the product, and the different source of the starting materials, such as in the case of autologous advanced therapy medicinal products, is not sufficient to support a claim that two products are not similar; or

(b) there are differences in the manufacturing technology having a significant impact on the biological characteristics or the biological activity relevant for the intended therapeutic effect or safety attributes of the product.

(3) In relation to gene therapy medicinal products—

(a) two gene therapy medicinal products are not to be considered similar when there are differences in the therapeutic sequence, viral vector, transfer system, regulatory sequences or manufacturing technology which significantly affect the biological characteristics or biological activity relevant for the intended therapeutic effect or safety attributes of the product; and

(b) differences in the therapeutic sequence with a significant impact on the intended therapeutic effect are not sufficient to support a claim that two gene therapy medicinal products are not similar.

(4) The considerations in paragraphs (2) and (3) also apply in relation to genetically modified cells.

8.—(1) This paragraph applies for the purposes of the definition of "similar active substance" in relation to radiopharmaceuticals.

(2) The same radiopharmaceutical active substance, or one differing from the original in radionuclide, ligand, site of labelling or molecule-radionuclide coupling mechanism linking the molecule and radionuclide which acts via the same mechanism, are to be considered similar substances.".

SCHEDULE 5

Regulation 73

Insertion of new Schedule 10A (variations to a UK marketing authorisation)

1. After Schedule 10, insert—

"SCHEDULE 10A

Regulation 65C(2)

Variations to a UK marketing authorisation

Interpretation

1. In this Schedule—

"change of, or addition of a new, route of administration", in relation to parenteral administration, includes any change or addition as between intra-arterial, intra-venous, intramuscular, subcutaneous and any other route;

"extension of a UK marketing authorisation" or "extension" means a variation which consists of—

(a) a change to one or more active substances that involves—

(i) replacement of a chemical active substance by a different salt, ester, complex or derivative, with the same therapeutic moiety, where the efficacy and safety characteristics are not significantly different,

(ii) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (for example, racemate by a single enantiomer), where the efficacy and safety characteristics are not significantly different,

(iii) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and safety characteristics are not significantly different, with the exception of changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza,

(iv) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy and safety characteristics are not significantly different,

(v) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy and safety characteristics are not significantly different, or

(vi) change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy and safety characteristics are not significantly different; or

(b) a change to strength, pharmaceutical form and route of administration that involves—

(i) change of bioavailability,

(ii) change of pharmacokinetics, for example change in rate of release,

(iii) change or addition of a new strength or potency,

(iv) change or addition of a new pharmaceutical form, or

(v) change or addition of a new route of administration;

"holder" means UK marketing authorisation holder;

"major variation of type II" means a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned namely—

(a) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

(b) variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings;

(c) variations related to changes outside the range of approved specifications, limits or acceptance criteria;

(d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;

(e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;

(f) variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with international scientific guidelines; or

(g) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

"minor variation of type IA" means a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned namely—

(a) variations of purely administrative nature that are related to the identity and contact details of—

(i) the holder,

(ii) the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or finished product;

(b) variations related to the identity, location and contact details of the qualified person for pharmacovigilance, or the location of the pharmacovigilance system master file;

(c) variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;

(d) variations related to minor changes to an approved physico-chemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former;

(e) variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the European Pharmacopoeia or of the British Pharmacopoeia, where the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties are unchanged;

(f) variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product;

(g) variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture;

"minor variation of type IB" means a variation which is not a minor variation of type IA, a major variation of type II nor an extension; and

"urgent safety restriction" means an interim change in the terms of the UK marketing authorisation due to new information having a bearing on the safe use of the medicinal product.

Classification of variations

2.—(1) Except where sub-paragraph (2) applies, a variation which is not an extension, and whose classification is undetermined after—

(a) application of the provisions in this Schedule; and

(b) taking into account—

(i) the guidance referred to in regulation 65C(4) or (6) as the case may be), and

(ii) where relevant, any recommendations delivered pursuant to paragraph 3,

is to be treated by the licensing authority as a minor variation of type IB.

(2) The licensing authority must treat a variation that would otherwise fall within sub-paragraph (1) as a major variation of type II in the following cases—

(a) upon request from the holder when submitting the variation; or

(b) where the licensing authority concludes, following the assessment of validity of a notification in accordance with paragraph 7(1), and taking into account the recommendations given under paragraph 3, that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.

Licensing authority recommendation on unclassified variations

3.—(1) Prior to the submission of a variation whose classification is not provided for in this Schedule—

(a) the holder may request a recommendation on the classification of the variation from the licensing authority; and

(b) the licensing authority must notify the holder of its recommendation within 45 days of that request, beginning with the date on which the request is received by the licensing authority.

(2) The 45-day period referred to in sub-paragraph (1)(b) may be extended by 25 days where the licensing authority deems it necessary.

Variations leading to the revision of product information

4. Where a variation leads to the revision of the summary of product characteristics, labelling or the package leaflet, the revision must be considered by the licensing authority as part of that variation.

Grouping of variations

5.—(1) Except where sub-paragraph (2) applies, where several variations are notified or applied for, a separate notification or application in accordance with paragraph 6, 7, 8 or 11 of this Schedule is to be submitted in respect of each variation sought.

(2) This sub-paragraph applies—

(a) where one or more of the same minor variations of type IA to the terms of one or more UK marketing authorisations owned by the same holder are notified at the same time to the licensing authority, in which case a single notification as referred to in paragraph 6 may cover all such variations;

(b) where several variations to the terms of the same UK marketing authorisation are submitted at the same time, a single submission may cover all such variations provided that the variations concerned fall within one of the relevant circumstances specified in sub-paragraph (3);

(c) where one or more of the same variation to the terms of one or more UK marketing authorisations held by the same holder are submitted at the same time and the variations do not fall within paragraph (a) or (b), a single submission may cover all such variations provided that the licensing authority agrees to such single submission.

(3) The relevant circumstances are—

(a) one of the variations in the group is an extension of the UK marketing authorisation;

(b) one of the variations in the group is a major variation of type II, but all other variations in the group are variations which are consequential to this major variation of type II;

(c) one of the variations in the group is a minor variation of type IB, but all other variations in the group are minor variations which are consequential to this minor variation of type IB;

(d) all variations in the group relate solely to changes of an administrative nature to the summary of product characteristics, labelling and package leaflet or insert;

(e) all variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File or Plasma Master File;

(f) all variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or one or more of its active substances;

(g) all variations in the group are changes affecting the quality of a human pandemic influenza vaccine;

(h) all variations in the group are changes to the pharmacovigilance system referred to in paragraph 12 of Schedule 8;

(i) all variations in the group are consequential to a given urgent safety restriction and submitted in accordance with paragraph 14;

(j) all variations in the group relate to the implementation of a given class labelling;

(k) all variations in the group are consequential to the assessment of a given periodic safety update report;

(l) all variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder;

(m) all variations in the group are consequential to a condition imposed under regulation 59(4C) or (4D).

(4) The submission referred to in sub-paragraph (2)(b) and (c) must be made by means of the following—

(a) a single notification in accordance with paragraph 7 where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;

(b) a single application in accordance with paragraph 8 where at least one of the variations is a major variation of type II and none of the variations is an extension; or

(c) a single application in accordance with paragraph 11 where at least one of the variations is an extension.

Notification procedure for minor variations of type IA

6.—(1) Subject to sub-paragraph (2), where a minor variation of type IA is made, the holder must submit to the licensing authority a notification containing the elements listed in paragraph 9 within 12 months, beginning with the date on which the variation is implemented by the holder.

(2) The notification referred to in sub-paragraph (1) must be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.

(3) Within 30 days beginning with the date on which the licensing authority receives a notification under this paragraph, the measures provided for in paragraph 10 are to be taken.

Notification procedure for minor variations of type IB

7.—(1) The holder must for minor variations of type IB submit to the licensing authority a notification containing the elements listed in paragraph 9, and if the notification contains those elements, the licensing authority must acknowledge receipt of a valid notification.

(2) If within 30 days beginning with the date on which the licensing authority acknowledges receipt of a valid notification, the licensing authority has not sent the holder an unfavourable opinion, the notification is deemed to be accepted by the licensing authority.

(3) Where the notification is accepted by the licensing authority, the measures provided for in paragraph 10 are to be taken.

(4) Where the licensing authority is of the opinion that the notification cannot be accepted, it must inform the holder, stating the grounds on which its unfavourable opinion is based.

(5) Within 30 days beginning with the date on which the holder receives the unfavourable opinion, the holder may submit to the licensing authority an amended notification in order to take due account of the grounds laid down in that opinion.

(6) If the holder does not amend the notification in accordance with sub-paragraph (5), the notification is deemed to be rejected.

(7) Where an amended notification has been submitted, the licensing authority must assess it within 30 days beginning with the date on which it receives the amended notification, and the measures provided for in paragraph 10 are to be taken.

(8) This paragraph does not apply where—

(a) a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension: in such a case, the prior approval procedure in paragraph 8 applies; or

(b) a type IB variation request is submitted in a grouping that includes an extension: in such a case, the procedure in paragraph 11 applies.

Prior approval procedure for major variations of type II

8.—(1) The holder must submit to the licensing authority an application containing the elements listed in paragraph 9, and if the application contains those elements, the licensing authority must acknowledge receipt of a valid application.

(2) Subject to sub-paragraph (3), within 60 days beginning with the date on which the licensing authority acknowledges receipt of a valid application under sub-paragraph (1), the licensing authority must conclude the assessment.

(3) The licensing authority may—

(a) reduce the period referred to in sub-paragraph (2), having regard to the urgency of the matter; or

(b) extend it to 90 days for—

(i) variations concerning a change to, or addition of, therapeutic indications, or

(ii) grouping of variations in accordance with paragraph 5(2)(c).

(4) Within the periods referred to in sub-paragraph (2) or (3), the licensing authority may request the holder to provide supplementary information within a time limit that it specifies, in which case—

(a) the procedure is suspended from the date on which such a request is made until the date on which that supplementary information has been provided; and

(b) the licensing authority may extend the period referred to in sub-paragraph (2) by the period for which the procedure is so suspended.

(5) Within 30 days beginning with the date on which the licensing authority concludes its assessment of the application, the measures provided for in paragraph 10 are to be taken.

(6) This paragraph does not apply where a type II variation request is submitted in a grouping that includes an extension: in such case, the procedure in paragraph 11 applies.

Elements to be submitted

9. An application or notification under this Schedule must include—

(a) a list of all the UK marketing authorisations affected by the notification or application;

(b) a description of all the variations submitted, including—

(i) in the case of minor variations of type IA, the date of implementation for each variation described,

(ii) in the case of minor variations of type IA which do not require immediate notification, a description of all minor variations of type IA made in the last 12 months to the terms of any affected UK marketing authorisation, such period beginning with the day on which the application or notification is submitted, and which have not been already notified,

(iii) any documents specified in guidance published under regulation 65C(4) or (6) (as the case may be), insofar as relevant to the type of variation notified or applied for,

(iv) where a variation leads to or is the consequence of other variations to the terms of the same UK marketing authorisation, a description of the relationship between those variations, and

(v) the relevant fee provided for in the Fees Regulations.

Measures to close the procedures specified in paragraphs 6 to 8

10. Where reference is made to this paragraph, the licensing authority must take the following measures—

(a) inform the holder as to whether the variation is accepted or rejected;

(b) where the variation is rejected, inform the holder of the grounds for the rejection; and

(c) where necessary, amend the decision granting the UK marketing authorisation in accordance with the accepted variation within the time limit laid down in paragraph 15.

Extensions of marketing authorisations

11.—(1) An application for an extension of a UK marketing authorisation must be assessed by the licensing authority in accordance with the same or equivalent procedure that applied under Part 5 to the initial UK marketing authorisation to which it relates.

(2) An extension must either be granted a UK marketing authorisation in accordance with the same or equivalent procedure as for the granting of the initial UK marketing authorisation to which it relates, or be included in that initial UK marketing authorisation.

Human influenza vaccines

12.—(1) By way of exception from paragraph 8, the procedure laid down in sub-paragraphs (2) to (4) applies to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.

(2) The holder must submit to the licensing authority an application containing the elements listed in paragraph 9, and if it does so, the licensing authority must acknowledge receipt of a valid application.

(3) The licensing authority must assess the application submitted, and where it deems it necessary, the licensing authority may request additional data from the holder in order to complete its assessment.

(4) The licensing authority must—

(a) adopt a decision within 45 days, beginning with the date on which it receives a valid application; and

(b) take the measures provided for in paragraph 10.

(5) The 45-day period referred to in sub-paragraph (4) is to be suspended from the date on which the additional data referred to in sub-paragraph (3) is requested until the date on which that data is received by the licensing authority.

Pandemic situation with respect to human influenza

13.—(1) By way of exception to the provisions of this Schedule, where a pandemic situation with respect to human influenza is duly recognised by the World Health Organisation, or the licensing authority, the licensing authority may exceptionally and temporarily accept a variation to the terms of a UK marketing authorisation for a human influenza vaccine, where certain non-clinical or clinical data are missing.

(2) Where a variation is accepted pursuant to sub-paragraph (1), the holder must submit the missing non-clinical and clinical data within a time limit set by the licensing authority.

Urgent safety restrictions

14.—(1) Where, in the event of a risk to public health, the holder takes urgent safety restrictions on its own initiative, it must forthwith notify the licensing authority.

(2) If the licensing authority has not raised objections within 24 hours following receipt of that information, the urgent safety restrictions are deemed to be accepted.

(3) In the event of a risk to public health in relation to a medicinal product, the licensing authority may impose urgent safety restrictions on the holder of the UK marketing authorisation in respect of that product.

(4) Where an urgent safety restriction is taken by the holder, or imposed by the licensing authority, the holder must submit the corresponding application for variation within 15 days beginning with the date on which that restriction is initiated.

Amendments to the decision granting the marketing authorisation

15.—(1) Amendments to the decision granting the UK marketing authorisation resulting from the procedures laid down in this Schedule must be made by the licensing authority—

(a) in the case of major variations of type II, within two months, beginning with the date on which the information referred to in paragraph 10(a) is sent to the holder; or

(b) in the other cases, within six months, beginning with the date on which the information referred to in paragraph 10(a) is sent to the holder,

and the licensing authority must notify the holder of the amended decision without delay.

(2) The statement indicating compliance with the agreed completed paediatric investigation plan provided for under regulation 58A(2)(a) must be included within the technical dossier of the UK marketing authorisation, and the licensing authority must confirm to the holder that it is so included when it notifies the holder under paragraph 10(a).

Implementation of variations

16.—(1) Minor variations of type IA may be implemented any time before completion of the procedures laid down in paragraph 6.

(2) Where a notification concerning one or several minor variations of type IA is rejected, the holder must cease to apply the rejected variation immediately after receipt of the information referred to in paragraph 10(a).

(3) Minor variations of type IB may only be implemented after the licensing authority has informed the holder that it has accepted the notification pursuant to paragraph 7, or after the notification is deemed accepted pursuant to paragraph 7(2).

(4) Major variations of type II may only be implemented after the licensing authority has informed the holder that it has accepted the variation pursuant to paragraph 10.

(5) An extension may only be implemented after the licensing authority has amended the decision granting the marketing authorisation and notified the holder accordingly.

(6) Urgent safety restrictions, and variations which are related to safety issues, must be implemented within a time frame agreed by the holder and the licensing authority.

Continuous monitoring

17. Where requested to do so by the licensing authority, the holder must supply to the licensing authority without delay any information related to the implementation of a given variation.".

SCHEDULE 6 Regulation 168

Insertion of new Schedule 12A (further provision as to the performance of pharmacovigilance activities)

1. After Schedule 12 insert—

"SCHEDULE 12A Regulation 205A

Further provision as to the performance of pharmacovigilance activities

PART 1

Pharmacovigilance system master file

Structure of the pharmacovigilance system master file

1.—(1) The information in the pharmacovigilance system master file must be accurate and reflect the pharmacovigilance system in place.

(2) The holder may, where appropriate, use separate pharmacovigilance systems for different categories of medicinal products and if it does so, each such system must be described in a separate pharmacovigilance system master file.

(3) All medicinal products for which the holder obtained a UK marketing authorisation in accordance with these Regulations must be covered by a pharmacovigilance system master file.

Content of the pharmacovigilance system master file

2. The pharmacovigilance system master file must, as a minimum, contain—

(a) the following information relating to the qualified person responsible for pharmacovigilance—

(i) a description of the responsibilities demonstrating that the qualified person for pharmacovigilance has sufficient authority over the pharmacovigilance system

in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities,

(ii) a summary curriculum vitae of the qualified person responsible for pharmacovigilance,

(iii) contact details of the qualified person for pharmacovigilance, and

(iv) details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;

(b) a description of the organisational structure of the holder, including the list of each site where one or more of the following pharmacovigilance activities are undertaken—

(i) individual case safety report collection and evaluation,

(ii) safety database case entry,

(iii) periodic safety update report production,

(iv) signal detection and analysis,

(v) risk management plan management,

(vi) pre and post-authorisation study management, and

(vii) management of safety variations to the terms of a UK marketing authorisation;

(c) a description of the location of, functionality of and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information, and an assessment of their fitness for purpose;

(d) a description of data handing and recording and of the process used for each of the following pharmacovigilance activities—

(i) the continuous monitoring of the risk-benefit balance of each medicinal product, the result of that monitoring and the decision-making process for taking appropriate measures,

(ii) operation of each risk management system and of the monitoring of the outcome of risk minimisation measures,

(iii) collection, assessment and reporting of individual case safety reports,

(iv) drafting and submission of periodic safety update reports, and

(v) procedures for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to healthcare professionals and the general public;

(e) a description of the quality system for the performance of pharmacovigilance activities, including—

(i) a description of—

(aa) the organisational structure for the performance of pharmacovigilance activities,

(bb) a summary description of the training concept, including a reference to the location of training files and qualifications records, and

(cc) instructions on critical processes,

(ii) a description of the record management system referred to in paragraph 12, including the location of the documents used for pharmacovigilance activities,

(iii) a description of the system for monitoring the performance of the pharmacovigilance system; and

(f) where applicable, a description of the activities or services subcontracted by the holder.

Content of the Annex to the pharmacovigilance system master file

3. The pharmacovigilance system master file must have an Annex containing the following documents—

(a) a list of medicinal products covered by the pharmacovigilance system master file, including the name of each medicinal product, the international non-proprietary name (INN) of each active substance and the countries other than the United Kingdom in which the products covered are authorised to be marketed;

(b) a list of written policies and procedures for the purpose of complying with Part 11 of these Regulations;

(c) the list of any sub-contracts falling within paragraph 6(1);

(d) a list of the tasks that have been delegated by the qualified person for pharmacovigilance;

(e) a list of all scheduled and completed audits;

(f) where applicable, a list of the performance indicators that support the quality system for pharmacovigilance specified in paragraph 2(e);

(g) where applicable, a list of other pharmacovigilance system master files held by the same holder; and

(h) a logbook containing a record of any alteration of the content of the pharmacovigilance system master file made within the preceding 5 year period, except any alteration of the content that is specified in of paragraph 2(a)(ii) to (iv) or this paragraph.

Maintenance of the pharmacovigilance system master file

4.—(1) The holder must keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, and of technical and scientific progress.

(2) The pharmacovigilance system master file and its Annex must be subject to version control and, in particular, must indicate the date when it was last updated by the holder.

(3) Any deviations from the pharmacovigilance procedures, their impact and their management must be documented in the pharmacovigilance system master file until resolved.

(4) Without prejudice to the requirements set out in regulation 65C and Schedule 10A (variations to a UK marketing authorisation), the holder must notify the licensing authority immediately of any change—

(a) in the location of the pharmacovigilance system master file; or

(b) to the contact details and name of the qualified person responsible for pharmacovigilance.

Form of the documents contained in the pharmacovigilance system master file

5.—(1) The pharmacovigilance system master file documents must be complete and legible.

(2) Subject to sub-paragraph (1), in the pharmacovigilance system master file—

(a) where appropriate, information may be provided in the form of charts or flow diagrams;

(b) all documents must be indexed and archived so as to ensure their accurate and ready retrieval throughout the period for record-keeping; and

(c) the particulars and documents may be presented in modules in accordance with the system delineated in detail in the guidance on good pharmacovigilance practices which applies by virtue of regulation 205B.

(3) The pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time, and a clearly arranged printed copy can be made available for audits and inspections.

Subcontracting

6.—(1) The holder may subcontract certain activities of the pharmacovigilance system to third parties, but if it does so it must nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

(2) The holder must draw up a list of the existing subcontracts between it and the third parties referred to in sub-paragraph (1), specifying each product and each country concerned.

Availability and location of the pharmacovigilance system master file

7.—(1) The pharmacovigilance system master file must be—

(a) located in, or accessible electronically from, the United Kingdom at the single point from which the reports referred to in regulation 187(4) are accessible; and

(b) permanently and immediately available for inspection at that single point in the United Kingdom.

(2) The holder must ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.

(3) For the purposes of regulation 182(2)(b), the licensing authority may limit its request to specific parts or modules of the pharmacovigilance system master file and the holder is to bear the costs of submitting the copy of the pharmacovigilance system master file.

(4) The licensing authority may request the holder to submit a copy of the logbook referred to in paragraph 3(h) at regular intervals.

PART 2

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by the licensing authority and holders

Quality system

8.—(1) Any holder, and the licensing authority, must establish and use a quality system that is adequate and effective for the performance of their pharmacovigilance activities.

(2) The quality system must cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.

(3) The quality system must be based on all of the following activities—

(a) quality planning: establishing structures and planning integrated and consistent processes;

(b) quality adherence, namely carrying out tasks and responsibilities in accordance with quality requirements;

(c) quality control and assurance, namely monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and

(d) quality improvements, namely correcting and improving the structures and processes where necessary.

(4) All elements, requirements and provisions adopted for the quality system must be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.

(5) All persons involved in the procedures and processes of the quality systems established by the licensing authority for the performance of pharmacovigilance activities shall be responsible for the good functioning of those quality systems, and must ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system.

Performance indicators

9.—(1) The holder and the licensing authority may use performance indicators to continuously monitor the good performance of pharmacovigilance activities.

(2) The licensing authority may publish a list of performance indicators.

PART 3

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by holders

Management of human resources

10.—(1) The holder must have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities.

(2) For the purposes of sub-paragraph (1), the holder must—

(a) ensure that the qualified person responsible for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities; and

(b) where the qualified person has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications, ensure that the qualified person responsible for pharmacovigilance is assisted by a medically trained person, with such assistance being duly documented.

(3) The duties of the managerial and supervisory staff, including the qualified person responsible for pharmacovigilance, must be defined in job descriptions and their hierarchical relationships must be defined in an organisational chart.

(4) The holder must ensure that the qualified person responsible for pharmacovigilance has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the holder.

(5) All personnel involved in the performance of pharmacovigilance activities must receive initial and continued training in relation to their role and responsibilities, and the holder must keep training plans and records for documenting, maintaining and developing the competences of personnel and make them available for audit or inspection.

(6) The holder must provide appropriate instructions on the processes to be used in case of urgency, including business continuity.

Compliance management

11.—(1) Specific quality system procedures and processes must be in place in order to ensure the following—

(a) the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the holder;

(b) the scientific evaluation by the holder of all information on the risks of medicinal products, as referred to in regulation 182(4)(a);

(c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the licensing authority within the time limits provided for in regulation 188(1)(a) or (b);

(d) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions;

(e) effective communication by the holder with the licensing authority, including communication on—

(i) new risks or changed risks,

(ii) the pharmacovigilance system master file,

(iii) risk management systems,

(iv) risk minimisation measures,

(v) periodic safety update reports,

(vi) corrective and preventive actions, and

(vii) post-authorisation studies;

(f) the update of product information by the holder in the light of scientific knowledge, including the assessments and recommendations made public via the UK web-portal, and on the basis of a continuous monitoring by the holder of information published on that web-portal; and

(g) appropriate communication by the holder of relevant safety information to healthcare professionals and patients.

(2) Where a holder has subcontracted some of its pharmacovigilance tasks, it must retain responsibility for ensuring that an effective quality system is applied in relation to those tasks.

Record management and data retention

12.—(1) A holder must record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

(2) A holder must put in place a record management system for all documents used for pharmacovigilance activities that ensures—

(a) the retrievability of those documents; and

(b) the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

(3) A holder must establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

(4) A holder must arrange for the elements referred to in sub-paragraph (2) to be kept for at least five years, beginning with the day after the system as described in the pharmacovigilance system master file has been formally terminated by the holder.

(5) Pharmacovigilance data and documents relating to individual authorised medicinal products must be retained as long as the product is authorised and for at least 10 years, beginning with the date on which the UK marketing authorisation ceased to exist.

Audit

13.—(1) Risk-based audits of the quality system must be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in paragraphs 8, 10, 11 and 12, and to determine its effectiveness.

(2) The audits referred to in sub-paragraph (1) must be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited.

(3) Following a risk-based audit—

(a) any corrective action, including a follow-up audit of deficiencies, must be taken where necessary;

(b) a report on the results of the audit must be drawn up for each audit and follow-up audit;

(c) the audit report must be sent to the management responsible for the matters audited; and

(d) the dates and results of audits and follow-up audits must be documented in accordance with regulation 184(1)(b).

PART 4

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by the licensing authority

Management of human resources

14.—(1) The licensing authority must have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities: the organisational structures and the distribution of tasks and responsibilities must be clear and, to the extent necessary, accessible.

(2) Named contact points in the licensing authority for pharmacovigilance activities must be established.

(3) The licensing authority must ensure that—

(a) all of its personnel involved in the performance of pharmacovigilance activities receive initial and continued training;

(b) it keeps training plans and records for documenting, maintaining and developing the competences of personnel; and

(c) such plans and records are available for audit.

(3) The licensing authority must ensure that it provides to its personnel performing pharmacovigilance activities appropriate instructions on the processes to be used in case of urgency, including business continuity.

Compliance management

15. The licensing authority must establish specific procedures and processes in order to achieve the following objectives—

(a) ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;

(b) ensuring the assessment of pharmacovigilance data and its processing within the timelines provided for in Part 11 of these Regulations;

(c) ensuring independence in the performance of pharmacovigilance activities;

(d) ensuring effective communication among regulatory bodies in countries other than the United Kingdom who have the same or similar functions as the licensing authority, as well as with patients, healthcare professionals, marketing authorisation holders and the general public; and

(e) conducting inspections, including pre-authorisation inspections.

Record management and data retention

16.—(1) The licensing authority must—

(a) record all pharmacovigilance information, and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information; and

(b) put in place a record management system for all documents used for pharmacovigilance activities that ensures—

(i) the retrievability of those documents, and

(ii) the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

(3) The licensing authority must arrange for the essential documents describing their pharmacovigilance system to be kept for at least five years, such period beginning with the day after the system has been formally terminated.

(4) Pharmacovigilance data and documents relating to individual authorised medicinal products must be retained by the licensing authority for as long as the product is authorised and for at least 10 years, such period beginning with the day after the UK marketing authorisation has expired.

Audit

17.—(1) Risk-based audits of the quality system must be performed by the licensing authority at regular intervals to ensure that the quality system complies with the requirements set out in paragraphs 8, 14, 15 and 16, and to ensure its effectiveness.

(2) Following a risk-based audit—

(a) any corrective action, including a follow-up audit of deficiencies, must be taken where necessary;

(b) a report on the results of the audit must be drawn up for each audit and follow-up audit;

(c) the audit report must be sent to the management responsible for the matters audited; and

(d) the dates and results of audits and follow-up audits must be documented.

PART 5

Use of terminology, formats and standards

Use of internationally agreed terminology, formats and standards

18. The licensing authority may publish a list of which of the internationally agreed—

(a) terminology; and

(b) formats and standards,

are to be used for the description, classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information.

PART 6

Transmission of reports of suspected adverse reactions

Individual case safety reports

19. Individual case safety reports must be used for reporting to the licensing authority suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time.

Content of the individual case safety report

20.—(1) Holders must—

(a) ensure that individual case safety reports are as complete as possible; and

(b) communicate the updates of those reports to the licensing authority in an accurate and reliable manner.

(2) In the case of expedited reporting, the individual case safety report must include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and any medicinal product concerned.

(3) Holders and the licensing authority must record the details necessary for obtaining follow-up information on individual case safety reports and such reports must be adequately documented.

(4) When reporting suspected adverse reactions, holders must provide all available information on each individual case, including—

(a) administrative information, namely—

(i) report type, date and a worldwide unique case identification number as well as unique sender identification and sender type,

(ii) the date on which the report was first received from the source and the date of receipt of the most recent information, using a precise date, and

(iii) other case identifiers and their sources, as well as references to additional available documents held by the sender of the individual case safety report, where applicable;

(b) literature reference in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors(**14**) for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article;

(c) study type, study name and the sponsor's study number or study registration number for reports from studies not covered by the Clinical Trials Regulations;

(d) information on any primary source, namely information identifying the reporter, including country of residence and professional qualifications;

(**14**) International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15.

(e) information identifying the patient (and parent in the case of a parent-child report), including age at the time of the onset of the first reaction, age group, gestation period when reaction or event was observed in the foetus, weight, height or gender, last menstrual date and, where relevant, gestation period at time of exposure;

(f) relevant medical history and concurrent conditions;

(g) the name of any medicinal product suspected to be related to the occurrence of the adverse reaction, including interacting medicinal products or, where the name is not known, any active substance and any other characteristics that allow for the identification of a medicinal product, including—

(i) the name of the holder, UK marketing authorisation number, pharmaceutical form and each (parent) route of administration,

(ii) any indication for use in the case, dose administered, start date and end date of administration,

(iii) actions taken with any medicinal product, and

(iv) effect of the dechallenge and rechallenge for suspect medicinal products;

(h) for a biological medicinal product, the batch number;

(i) concomitant medicinal products, identified in accordance with paragraph (g), which are not suspected to be related to the occurrence of the adverse reaction and past-medical drug therapy for the patient (and for the parent), where applicable;

(j) information on any suspected adverse reaction, including—

(i) start date and end date of any suspected adverse reaction or duration,

(ii) seriousness,

(iii) outcome of any suspected adverse reaction at the time of last observation,

(iv) time intervals between suspect medicinal product administration and start of any adverse reaction,

(v) the original reporter's words or short phrases used to describe any reaction, and

(vi) country of occurrence of the suspected adverse reaction;

(k) results of tests and procedures relevant to the investigation of the patient;

(l) in the event of death of the patient, date and reported cause of death, including autopsy-determined causes;

(m) a case narrative, where possible, providing all relevant information for individual cases with the exception of non-serious adverse reactions; and

(n) reasons for nullifying or amending an individual case safety report.

(5) For the purposes of—

(a) sub-paragraph (4)(b), upon request of the licensing authority, the holder that transmitted the initial report must provide a copy of the relevant article taking into account copyright restrictions, and a full translation of that article into English;

(b) sub-paragraph (4)(h), a follow-up procedure must be in place to obtain the batch number where it is not indicated in the initial report;

(c) sub-paragraph (4)(m), the information must be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained: any relevant autopsy or post-mortem findings must also be summarised in the narrative.

(6) Suspected adverse reactions must be reported in English.

Format of electronic transmission of suspected adverse reactions

21. Holders must use the formats and terminology specified in the list published under paragraph 18 for the electronic transmission of suspected adverse reactions, if the licensing authority has published a list under that paragraph.

PART 7

Risk management plans

Content of the risk management plan

22.—(1) The risk management plan established by the holder must contain the following elements—

(a) an identification or characterisation of the safety profile of the medicinal product concerned;

(b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned;

(c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those measures; and

(d) a documentation of post-authorisation obligations that have been imposed as a condition of the UK marketing authorisation.

(2) Medicinal products may, where appropriate be subject to the same risk management plan if they—

(a) contain the same active substance; and

(b) belong to the same holder.

(3) Where a risk management plan refers to post-authorisation studies—

(a) it must indicate whether those studies are initiated, managed or financed by the holder voluntarily, or pursuant to obligations imposed by the licensing authority or an equivalent authority to the licensing authority in another country; and

(b) all post-authorisation obligations must be listed in the summary of the risk management plan referred to in paragraph 23, together with a timeframe for meeting those obligations.

Summary of the risk management plan

23.—(1) The summary of the risk management plan to be made publicly available in accordance with regulation 203(2)(d) (obligations on licensing authority in relation to national medicines web-portal) must include key elements of the risk management plan with a specific focus on risk minimisation activities and, with regard to the safety specification of the medicinal product concerned, important information on potential and identified risks as well as missing information.

(2) Where a risk management plan concerns more than one medicinal product, a separate summary of the risk management plan must be provided by holders for each medicinal product.

Updates of the risk management plan

24.—(1) Subject to sub-paragraph (2), where the holder updates a risk management plan, it must submit the updated risk management plan to the licensing authority.

(2) If the licensing authority agrees, the holder may submit only the modules concerned by the update.

(3) If necessary, the holder must provide the licensing authority with an updated summary of the risk management plan.

(4) Each submission of the risk management plan must—

(a) have a distinct version number; and

(b) be dated.

Format of the risk management plan

25. The risk management plan must be in the following format—

(a) Part I: product overview;

(b) Part II: safety specification consisting of—

(i) Module SI: epidemiology of each indication and each target population,

(ii) Module SII: non-clinical part of the safety specification,

(iii) Module SIII: clinical trial exposure,

(iv) Module SIV: populations not studied in clinical trials,

(v) Module SV: post-authorisation experience,

(vi) Module SVI: additional EU requirements for the safety specification,

(vii) Module SVII: identified and potential risks, and

(viii) Module SVIII: summary of the safety concerns;

(c) Part III: pharmacovigilance plan, including post-authorisation safety studies;

(d) Part IV: plans for post-authorisation efficacy studies;

(e) Part V: risk minimisation measures, including evaluation of the effectiveness of risk minimisation activities;

(f) Part VI: summary of the risk management plan; and

(g) Part VII: annexes.

PART 8

Periodic safety update reports

Content of periodic safety update reports

26.—(1) The periodic safety update report ("PSUR") must—

(a) be based on all available data; and

(b) focus on new information which has emerged since the data lock point of the last PSUR.

(2) The PSUR must provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions.

(3) The estimate of exposure referred to in sub-paragraph (2) must be accompanied by a qualitative and quantitative analysis of actual use, which must indicate, where appropriate, how actual use differs from the indicated use based on all data available to the holder, including the results of observational or drug utilisation studies.

(4) The PSUR must contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment.

(5) Where any conditions are imposed under regulation 59(4A) (conditions in relation to UK marketing authorisations to which paediatric specific provisions apply) or 59(4D) (conditions in relation to UK marketing authorisations for advanced therapy medicinal products), the PSUR must also include an assessment of the effectiveness of any risk management system, and the results of any studies performed, in order to comply with those conditions.

(6) Subject to sub-paragraph (7), holders are not required to include systematically detailed listings of individual cases, including case narratives, in the PSUR.

(7) Holders must provide case narratives in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern in the relevant risk evaluation section.

(8) Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the holder must draw conclusions in the PSUR as to the need for changes or actions, including implications for the approved summary of product characteristics for each product for which the PSUR is submitted.

(9) Unless otherwise agreed with the licensing authority, a single PSUR must be prepared for all medicinal products which—

(a) contain the same active substance; and

(b) are authorised for the same holder,

and sub-paragraph (10) applies to that single PSUR.

(10) Where this sub-paragraph applies—

(a) the PSUR must cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures; and

(b) where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen must be presented in a separate section of the PSUR, with any safety concerns addressed accordingly.

(11) Unless otherwise agreed with the licensing authority, if the substance that is the subject of the PSUR is also authorised as a component of a fixed combination medicinal product, the holder must either—

(a) submit a separate PSUR for the combination of active substances authorised for the same holder, with cross-references to each relevant single-substance PSUR; or

(b) provide the combination data within one of the single-substance PSURs.

Format of periodic safety update reports

27. Electronic PSURs must be submitted in the following format—

(a) Part I: title page including signature;

(b) Part II: executive summary; and

(c) Part III: table of contents which contains—

(i) introduction,

(ii) worldwide marketing authorisation status,

(iii) actions taken in the reporting interval for safety reasons,

(iv) changes to reference safety information,

(v) estimated exposure and use patterns—

(aa) cumulative subject exposure in clinical trials,

(bb) cumulative and interval patient exposure from marketing experience,

(vi) data in summary tabulations—

(aa) reference information,

(bb) cumulative summary tabulations of serious adverse events in clinical trials,

(cc) cumulative and interval summary tabulations from post-marketing data sources,

(vii) summaries of significant findings from clinical trials during the reporting interval—

(aa) completed clinical trials,

(bb) ongoing clinical trials,

(cc) long-term follow-up,

(dd) other therapeutic use of medicinal product,

(ee) new safety data related to fixed combination therapies,

(viii) findings from non-interventional studies,

(ix) information from other clinical trials and sources,

(x) non-clinical data,

(xi) literature,

(xii) other periodic reports,

(xiii) lack of efficacy in controlled clinical trials,

(xiv) late-breaking information,

(xv) overview on signals: new, ongoing or closed,

(xvi) signal and risk evaluation—

(aa) summaries of safety concerns,

(bb) signal evaluation,

(cc) evaluation of risks and new information,

(dd) characterisation of risks, and

(ee) effectiveness of risk minimisation (if applicable),

(xvii) benefit evaluation—

(aa) important baseline efficacy and effectiveness information,

(bb) newly identified information on efficacy and effectiveness, and

(cc) characterisation of benefits,

(xviii) integrated benefit-risk analysis for authorised indications—

(aa) benefit-risk context: medical need and important alternatives, and

(bb) benefit-risk analysis evaluation,

(xix) conclusions and actions, and

(xx) appendices to the PSUR.

PART 9

Post-authorisation safety studies

Scope and interpretation

28.—(1) This Part applies to non-interventional post-authorisation safety studies initiated, managed or financed by a holder under obligations imposed under regulation 59 or 61 (conditions of UK marketing authorisation).

(2) In this Part—

"start of data collection" means the date on which information on the first study subject is first recorded in the study dataset or, in the case of the secondary use of data, the date on which the data extraction starts; and

"end of data collection" means the date on which the analytical dataset is completely available.

Obligations as to post-authorisation safety studies

29.—(1) The holder must submit in English—

(a) the study protocol; and

(b) the abstract of the final study report and the final study report.

(2) The holder must ensure that—

(a) all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information;

(b) the confidentiality of the records of the study subjects remains protected; and

(c) the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

(3) The licensing authority may publish appropriate templates for the protocol, abstract and final study report.

Format of the study protocol

30. The study protocol for a non-interventional post-authorisation safety studies must be submitted in the following format—

(a) title: informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version;

(b) name of holder;

(c) responsible parties including a list of all collaborating institutions and other relevant study sites.

(d) abstract, which must consist of a stand-alone summary of the study protocol, including the following subsections—

(i) title with subtitles including version and date of the protocol and name and affiliation of the main author,

(ii) rationale and background,

(iii) research question and objectives,

(iv) study design,

(v) population,

(vi) variables,

(vii) data sources,

(viii) study size,

(ix) data analysis, and

(x) milestones;

(e) amendments and updates, namely any substantial amendment and update to the study protocol after the start of data collection, including a justification for the amendment or update, the date of the change, and a reference to the section of the protocol where the change has been made.

(f) milestones, namely a table with planned dates for the following milestones—

(i) start of data collection,

(ii) end of data collection,

(iii) any study progress report as referred to in regulation 198(2),

(iv) any interim report of study results, if applicable, and

(v) final report of study results;

(g) rationale and background, namely a description of any safety hazard, the safety profile or the risk management measures that led to the study being imposed as an obligation for a UK marketing authorisation;

(h) research question and objectives in accordance with the decision of the licensing authority in imposing the study as an obligation;

(i) research methods, namely a description of the research methods, including—

(i) study design,

(ii) setting, namely the study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria: where any sampling from a source population is undertaken, a description of the source population and details of sampling methods must be provided and where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies must be explained,

(iii) variables,

(iv) data sources, namely strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives: where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data must be reported and in the case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators must be described,

(v) study size, namely any projected study size, precision sought for study estimates and any calculation of the study size that can minimally detect a pre-specified risk with a pre-specified interpretative power,

(vi) data management,

(vii) data analysis,

(viii) quality control, and

(ix) limitations of the research methods;

(j) protection of human subjects, namely safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies;

(k) management and reporting of adverse events or adverse reactions and other medically important events while the study is being conducted;

(l) plans for disseminating and communicating study results; and

(m) references.

Format of the abstract of the final study report

31. The abstract of the final study report for a non-interventional post-authorisation safety studies must be submitted in the following format—

(a) title, with subtitles including date of the abstract and name and affiliation of main author;

(b) keywords (not more than five keywords indicating the main study characteristics);

(c) rationale and background;

(d) research question and objectives;

(e) study design;

(f) setting;

(g) subjects and study size, including dropouts;

(h) variables and data sources;

(i) results;

(j) discussion (including, where relevant, an evaluation of the impact of study results on the risk–benefit balance of the product);

(k) name of holder; and

(l) names and affiliations of principal investigators.

Format of the final study report

32. The final study report for a non-interventional post-authorisation safety studies must be submitted in the following format—

(a) title, including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of the main author;

(b) abstract, namely a stand-alone summary referred to in paragraph 31;

(c) name and address of the holder;

(d) investigators, namely the names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites;

(e) milestones, namely the dates for the following milestones—

(i) start of data collection (planned and actual dates),

(ii) end of data collection (planned and actual dates),

(iii) study progress reports,

(iv) interim reports of study results, where applicable,

(v) final report of study results (planned and actual date), and

(vi) any other important milestone applicable to the study, including date of study registration in the electronic study register

(f) rationale and background, namely a description of the safety concerns that led to the study being initiated, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill;

(g) research question and objectives;

(h) amendments and updates to the protocol, namely a list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update;

(i) research methods, namely—

(i) study design: key elements of the study design and rationale for this choice,

(ii) setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection: in the case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale,

(iii) subjects: any source population and eligibility criteria for study subjects. Sources and methods for selection of participants shall be provided, including, where relevant, methods for case ascertainment, as well as number of and reasons for dropouts,

(iv) variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions: diagnostic criteria shall be provided, where applicable,

(v) data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement; if the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data must be reported and in the case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators,

(vi) bias,

(vii) study size: study size, rationale for any study size calculation and any method for attaining projected study size,

(viii) data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why,

(ix) statistical methods: description of the following items—

(aa) main summary measures,

(bb) all statistical methods applied to the study,

(cc) any methods used to examine subgroups and interactions,

(dd) how missing data were addressed,

(ee) any sensitivity analyses, and

(ff) any amendment to the plan of data analysis included in the study protocol, with rationale for the change, and

(x) quality control: mechanisms to ensure data quality and integrity;

(j) results: comprising the following subsections—

(i) participants, namely numbers of study subjects at each stage of study: in the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage,

(ii) descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data. In the case of a systematic review or meta-analysis, characteristics of each study from which data were extracted,

(iii) outcome data: numbers of study subjects across categories of main outcomes,

(iv) main result: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision and where relevant, estimates of relative risk must be translated into absolute risk for a meaningful time period,

(v) other analyses, and

(vi) adverse events and adverse reactions;

(k) discussion which must include—

(i) key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, the impact of the results on the risk–benefit balance of the product,

(ii) limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them, sources of potential bias and imprecision, and validation of the events; both the direction and magnitude of potential biases must be discussed,

(iii) interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence, and

(iv) generalisability; and

(l) references.".

SCHEDULE 7

Regulation 228(2)

Insertion of new Schedule 33A (transitional provision)

1. After Schedule 33 insert—

"SCHEDULE 33A

Regulation 347A

Transitional provision in relation to EU Exit

PART 1

Interpretation

1. In this Schedule—

"the COMP" means the Committee for Orphan Medicinal Products of the EMA, established under Article 4 of the Orphan Regulation;

"converted EU marketing authorisation" has the meaning given in paragraph 6(1) and (2);

"the Paediatric Regulation" means Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, as it has effect in EU law(**15**);

"the Paediatric Committee" means the committee of the EMA established under Article 3 of the Paediatric Regulation;

"the Pharmacovigilance Risk Assessment Committee" means the Committee of the EMA established by Article 56(1)(aa) of Regulation (EC) No 726/2004; and

"Regulation (EC) No 507/2006" means Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, as it has effect in EU law(**16**).

PART 2

Manufacturing, wholesale dealing and brokering

Wholesale dealer's licence used to distribute a medicinal product imported from an EEA State before exit day

2.—(1) Subject to sub-paragraphs (2) and (3), a person ("P") who is the holder of a wholesale dealer's licence which—

(a) was granted before exit day by the licensing authority;

(b) was in force immediately before exit day and remains in force on exit day (whether or not it is suspended); and

(c) was used by P to distribute a medicinal product, which was imported from an EEA State, by way of wholesale dealing, or to possess a medicinal product imported from an EEA State for such a purpose,

is deemed on and after exit day to hold a wholesale dealing licence granted under Part 3 (manufacture and distribution of medicinal products and active substances) that permits the operation of importing medicinal products from an approved country for import for the purposes specified in paragraph (c).

(2) After the end of the period of 6 months beginning with exit day, P is deemed to continue hold a wholesale dealer's licence that permits the operation of importing medicinal products from an approved country for import by virtue of sub-paragraph (1) only if, before the end of that period, P has notified the licensing authority in writing of—

(a) P's intention to continue to import medicinal products from an approved country for import; and

(b) either—

(i) P's intention to appoint a responsible person (import) who will carry out the functions under regulation 45AA(4) (requirement as to responsible persons where licence holder imports from an approved country for import) in respect of the licence, or

(ii) that P will only import medicinal products from an approved country for import to which an exemption in regulation 45AA(2) applies.

(**15**) OJ No. L 387, 27.12.2006, p. 1.
(**16**) OJ No. L 92, 30.3.2006, p. 6.

(3) Unless P has notified the licensing authority as provided for in sub-paragraph (2)(b)(ii), after the end of the period of 2 years beginning with exit day, P is deemed to continue to hold a wholesale dealer's licence that permits the operation of importing medicinal products from an approved country for import by virtue of sub-paragraph (1) only if, before the end of that period, P has notified the licensing authority in writing of the name, address and qualifications of a person who—

(a) is included in the register under regulation 45AB(1); and

(b) will carry out the functions under regulation 45AA(4) in respect of the licence.

(4) From exit day, until the date on which P notifies the licensing authority of the information specified in sub-paragraph (3), the responsible person in respect of that licence under regulation 45 must carry out the functions under regulation 45AA(4).

(5) As soon as reasonably practicable after receipt of the information specified in paragraph (3), the licensing authority must provide P with written notice that the responsible person (import) is named on the licence.

(6) Where P has notified the licensing authority as provided for in sub-paragraph (2)(b)(ii), the licensing authority must, as soon as reasonably practicable, notify P in writing that the wholesale dealer's licence includes import of a medicinal product from an approved country for import limited to medicinal products to which an exemption in regulation 45AA(2) applies.

Approved country for import list on exit day (regulation 18A)

3.—(1) For the purposes of regulation 18A(1) (approved country for import), during the transitional period, the licensing authority must publish an approved country for import list that includes each EEA State in it.

(2) The licensing authority must not, before the end of the transitional period, exercise its power under regulation 18A(3) to remove an EEA State from the approved country for import list.

(3) In this paragraph, "the transitional period" is the period of two years beginning with exit day.

Qualified persons and approved country for batch testing list on exit day (Schedule 7)

4.—(1) Sub-paragraph (2) applies to a person who—

(a) is acting as a qualified person immediately before exit day; and

(b) satisfies the requirements of Part 1 of Schedule 7 (qualification requirements for qualified persons) immediately before exit day as they had effect at that time.

(2) The person is to be treated on and after exit day as continuing to satisfy the requirements of Part 1 of Schedule 7 if the person would otherwise fail to do so as a result of amendments made to that Part by the EU Exit Regulations.

(3) For the purposes of paragraph 14(1)(b) of Schedule 7 (obligations of qualified person), for the transitional period, the licensing authority is deemed to have made appropriate arrangements with—

(a) each EEA State;

(b) Australia;

(c) Canada;

(d) Israel;

(e) Japan;

(f) New Zealand;

(g) Switzerland; and

(h) the United States of America,

and the licensing authority must, on exit day, publish a list that includes those countries under paragraph 14(3) of Schedule 7.

(4) The licensing authority may, in respect of any country specified in sub-paragraph (3)(b) to (h), include that country in the list subject to a condition or restriction as provided for in paragraph 14(4) of Schedule 7, insofar as that condition or restriction was reflected in the appropriate arrangements that existed immediately before exit day under Article 51(2) of the 2001 Directive.

(5) The licensing authority must not, before the end of the transitional period, exercise its powers under paragraph 14(6) of Schedule 7 to remove an EEA State from the list it publishes.

(6) In this regulation, "the transitional period" is the period of two years beginning with exit day.

List of countries with equivalent regulatory standards as to the manufacturing of active substances on exit day (regulation 45O(6) to (9))

5.—(1) For the purposes of regulation 45O(6) (requirements for registration as an importer, manufacturer or distributor of active substances), for the transitional period, the licensing authority must publish a list that includes the following countries—

(a) each EEA State;

(b) Australia;

(c) Brazil;

(d) Israel;

(e) Japan;

(f) Switzerland; and

(g) the United States of America.

(2) The licensing authority must not, before the end of the transitional period, exercise its power under regulation 45O(9) to remove an EEA State from the list it publishes.

(3) In this paragraph, "the transitional period" is the period of two years beginning with exit day.

PART 3

Transitional provision in respect of conversion of EU marketing authorisations in force immediately before exit day

Conversion of EU marketing authorisations in force before exit day

6.—(1) This paragraph applies in relation to an EU marketing authorisation which was in force immediately before exit day.

(2) An EU marketing authorisation to which this paragraph applies—

(a) has effect on and after exit day as a UK marketing authorisation granted under regulation 49(1) of these Regulations; and

(b) is referred to in this Part as a "converted EU marketing authorisation".

(3) If the holder of an EU marketing authorisation to which this paragraph applies notifies the licensing authority in writing before the end of the period of 21 days beginning with exit day that it does not wish to be the holder of a converted EU marketing authorisation, the licensing authority must revoke the converted EU marketing authorisation with effect from the date of receipt of the notification.

(4) A converted EU marketing authorisation—

(a) is treated as if it had been granted by the licensing authority under regulation 49(1) on the same terms as those on which the EU marketing authorisation was granted, including any conditions or restrictions subject to which the EU marketing authorisation was granted and which remain in force immediately before exit day;

(b) is treated, for the purposes of regulations 65 or 65B (validity of UK marketing authorisation), as if it had been granted by the licensing authority on the date that the EU marketing authorisation took effect;

(c) is treated for the purposes of regulation 67(1) (failure to place on the market) as if it had been granted on exit day, and the period of three years referred to in regulation 67(2) is treated as having started on exit day;

(d) is treated for the purposes of determining the relevant fee period for the purposes of Schedule 4 to the Fees Regulations (periodic fees for marketing authorisations) as if it had been granted by the licensing authority on the date that the EU marketing authorisation took effect;

(e) is treated, for the purposes of the reference to the date of grant in regulation 27A(a) of the Fees Regulations (fees for renewals of a marketing authorisation) as if it had been granted on the date that the EU marketing authorisation took effect;

(f) retains, for the purposes of regulation 51(1) and (2), the benefit of any remaining periods of data or marketing exclusivity (if any) from which the holder benefitted immediately before exit day;

(g) retains the benefit of any decision by the EMA to exempt the holder from Articles 14(4) or (5) of Regulation (EC) No 726/2004 (failure to place on the market), and that decision is treated as if it had been made by the licensing authority under regulation 67(3); and

(h) remains subject to—

(i) any suspension of the EU marketing authorisation that is in force immediately before exit day,

(ii) any post-authorisation obligations imposed after it was granted, and which remain in force immediately before exit day, and

(iii) any variation to its terms which were granted or accepted before exit day.

(5) For the purposes of this paragraph, an EU marketing authorisation is in force, even if that authorisation is suspended immediately before exit day.

(6) A converted EU marketing authorisation to which this paragraph applies which—

(a) was granted as a conditional marketing authorisation within the meaning of Article 1 of Regulation (EC) No 507/2006; and

(b) remains such a conditional marketing authorisation immediately before exit day,

has effect on and after exit day as a UK marketing authorisation granted under regulation 58F.

(7) A converted EU marketing authorisation to which this paragraph applies which relates to a medicinal product which—

(a) was designated as an orphan medicinal product by the European Commission pursuant to Article 5 of the Orphan Regulation; and

(b) remains in the Community register of Orphan Medicinal Products as referred to in that Article immediately before exit day,

has effect on and after exit day as a UK marketing authorisation granted under regulation 58C and retains, for the purposes of regulation 58D, the benefit of any period of marketing exclusivity from which the holder benefitted immediately before exit day under Article 8 of the Orphan Regulation.

Classification of converted EU marketing authorisations

7. For the purposes of regulation 62 (classification of UK marketing authorisation), it is a term of a converted EU marketing authorisation that the product to which the authorisation relates is to be available—

(a) in a case where the product was classified in its EU marketing authorisation immediately before exit day as a prescription only medicine, the product is to be available only on prescription;

(b) in a case where the product was not so classified and the licensing authority has determined that the product should be available on general sale, the product is to be available on general sale; or

(c) in any other case, the product is to be available only from a pharmacy.

Obligations of licensing authority in connection with converted EU marketing authorisations

8.—(1) The licensing authority must, before the end of the period of 7 days beginning with exit day, notify the holders of converted EU marketing authorisations—

(a) that the EU marketing authorisation is converted to a UK marketing authorisation; and

(b) that the holder may notify the licensing authority in accordance with paragraph 6(3) that it does not wish to be the holder of a UK marketing authorisation.

(2) The licensing authority must, as soon as reasonably practicable after the end of the period referred to in paragraph 6(3), publish a list of converted EU marketing authorisations.

(3) The list mentioned in sub-paragraph (2) must specify which converted EU marketing authorisations have been revoked in accordance with paragraph 6(3).

Obligations of holders of converted EU marketing authorisations

9.—(1) A holder of a converted EU marketing authorisation must submit to the licensing authority, before the end of the period of one year beginning with exit day, the information described in sub-paragraph (3).

(2) The obligation in sub-paragraph (1) is subject to any requirement imposed by the licensing authority to provide that information before the end of a shorter period specified by the licensing authority under paragraph 10(1).

(3) The information which must be submitted in accordance with sub-paragraph (1) (referred to in this paragraph as the "baseline data") is—

(a) such information concerning the product to which the converted EU marketing authorisation relates as may be specified in writing for this purpose and published by the licensing authority on or before exit day;

(b) notification of whether or not the product to which the converted EU marketing authorisation relates—

(i) is on the market in the United Kingdom at the time the notification is given, or

(ii) if not, whether the product has been on the market in the United Kingdom at any time on or after exit day and if so, the date on which it was withdrawn from the United Kingdom market.

(4) In this Part, the date on which the holder of a converted EU marketing authorisation complies with the obligation in sub-paragraph (1), or with any requirement imposed by the licensing authority under paragraph 10(1) to provide all of the baseline data before the end of a period shorter than the period of one year beginning with exit day, is referred to as "the data submission date".

Powers of licensing authority in connection with provision of information

10.—(1) If the licensing authority requests a holder of a converted EU marketing authorisation to submit all or part of the baseline data at any time before the expiry of the period of one year beginning with exit day, the holder must supply the information within the time period specified by the licensing authority in its request.

(2) If the licensing authority requests a holder of a converted EU marketing authorisation to provide any other information relating to the EU marketing authorisation, the holder must supply the information within the time period specified by the licensing authority in its request.

Variations of converted EU marketing authorisations notified or applied for before exit day

11.—(1) This paragraph applies where, before exit day—

(a) a holder of a converted EU marketing authorisation has notified the EMA of, or made an application to the EMA for, a variation of the EU marketing authorisation to which the converted EU marketing authorisation applies under Chapter III of Regulation (EC) No 1234/2008, or has made an application to the EMA for an extension of that EU marketing authorisation in accordance with Article 19 of that Regulation;

(b) the procedures specified in Article 17 of that Regulation (measures to close the procedures of Articles 14 to 16) have not concluded, or, in the case of an extension, no final decision has been made by the European Commission in relation to the application; and

(c) the holder of the converted EU marketing authorisation wishes the variation to be made to the converted EU marketing authorisation.

(2) Where the variation is a minor variation of Type IA—

(a) the variation may be implemented in relation to the converted EU marketing authorisation at any time on or after the time at which it may be implemented in relation to the EU marketing authorisation to which the converted EU marketing authorisation relates;

(b) the holder of the converted EU marketing authorisation must (subject to paragraph 13), include in the baseline data—

(i) a summary of the variation, and

(ii) if the notification has been rejected by the EMA, an indication of that fact; and

(c) the variation to the converted EU marketing authorisation is deemed to be accepted unless the licensing authority notifies the holder in writing before the end of the period of 30 days beginning with the data submission date that the variation is rejected, in which case the holder must cease to apply the rejected variation immediately after receipt of the notification.

(3) Where the variation is a minor variation of Type IB—

(a) the variation may be implemented in relation to the converted EU marketing authorisation at any time on or after the time at which it may be implemented in relation to the EU marketing authorisation to which the converted EU marketing authorisation relates;

(b) if the variation has not been rejected by the EMA, the holder of the converted EU marketing authorisation must (subject to paragraph 13) include a copy of the notification in the baseline data; and

(c) the variation to the converted EU marketing authorisation is deemed to be accepted unless the licensing authority notifies the holder in writing before the end of the period of 30 days beginning with the data submission date that the variation is rejected, in which case the holder must cease to apply the rejected variation immediately after receipt of the notification.

(4) Sub-paragraph (5) applies where—

(a) the variation is a major variation of Type II or an extension; and

(b) before exit day the Committee for Medicinal Products for Human Use gave a positive final opinion in relation to the application with which the United Kingdom concurred.

(5) Where this sub-paragraph applies—

(a) the variation may be implemented in relation to the converted EU marketing authorisation at any time on or after the time at which it may be implemented in relation to the EU marketing authorisation to which the converted EU marketing authorisation relates;

(b) the holder of the converted EU marketing authorisation must (subject to paragraph 13) include a copy of the application in the baseline data; and

(c) the licensing authority must either—

(i) treat the variation as accepted, and, if the variation affects the terms of the converted EU marketing authorisation, amend those terms accordingly; or

(ii) notify the holder of the converted EU marketing authorisation before the end of the period of 30 days beginning with the data submission date that the variation is rejected, in which case the holder must cease to apply the rejected variation immediately after receipt of the notification.

(6) Sub-paragraph (7) applies where—

(a) the variation is a major variation of Type II or an extension; and

(b) before exit day the Committee for Medicinal Products for Human Use had not given any opinion in relation to the application, or had given a negative final opinion in relation to it, or had given a positive final opinion but the United Kingdom recorded a divergent opinion.

(7) Where this paragraph applies—

(a) the holder of the converted EU marketing authorisation must submit to the licensing authority—

(i) the application for the variation; and

(ii) (subject to paragraph 13) the baseline data; and

(b) the licensing authority must consider the application in accordance with Schedule 10A.

(8) In this paragraph and paragraph 12, "minor variation of Type IA", "minor variation of Type IB", "major variation of Type II" and "extension" have the meanings given in paragraph 1 of Schedule 10A.

Variations of converted EU marketing authorisations submitted to EMA after exit day but before the data submission date

12.—(1) This paragraph applies where a holder of a converted EU marketing authorisation—

(a) notifies the EMA of, or applies to the EMA for, a variation of the EU marketing authorisation to which the converted EU marketing authorisation relates during the period beginning with exit day and ending on the day before the data submission date; and

(b) wishes the variation to be made in relation to the converted EU marketing authorisation.

(2) Where the variation is a minor variation of Type IA—

(a) the variation may be implemented in relation to the converted EU marketing authorisation at the same time as it may be implemented in relation to the EU marketing authorisation to which the converted EU marketing authorisation relates;

(b) the holder of the converted EU marketing authorisation must (subject to paragraph 13), include in the baseline data—

(i) a summary of the variation, and

(ii) if the notification has been rejected by the EMA, an indication of that fact; and

(c) the variation to the converted EU marketing authorisation is deemed to be accepted unless the licensing authority notifies the holder in writing within the period of 30 days beginning with the data submission date that the variation is rejected, in which case the holder must cease to apply the rejected variation immediately after receipt of the notification.

(3) Where the variation is a minor variation of Type IB, a major variation of Type II or an extension which has not been rejected by the EMA—

(a) the holder of the converted EU marketing authorisation must submit to the licensing authority—

(i) the notification of, or application for, the variation, and

(ii) (subject to paragraph 13) the baseline data; and

(b) the licensing authority must consider the application in accordance with Schedule 10A.

Variations of converted EU marketing authorisations sought in advance of the data submission date

13.—(1) If a holder of a converted EU marketing authorisation wishes the licensing authority to consider a notification of, or an application for, a variation to the authorisation before the data submission date, the holder must—

(a) submit the notification or application to the licensing authority; and

(b) unless sub-paragraph (2) applies, provide to the licensing authority at the same time such information concerning the product to which the converted EU marketing authorisation relates as may be specified in writing by the licensing authority for this purpose and published on or before exit day.

(2) If a holder of a converted EU marketing authorisation wishes the licensing authority to consider a notification of, or an application for, a variation to the authorisation before the data submission date but does not provide the information described in sub-paragraph (1)(b) with the notification or application, the licensing authority may agree to consider the notification or application if it is satisfied that—

(a) the variation may be necessary on urgent safety grounds;

(b) the variation may be necessary in order to maintain supplies of a particular medicinal product to patients in the United Kingdom; or

(c) there are other good reasons for considering the variation in advance of the submission of the information described in sub-paragraph (1).

(3) Where the licensing authority considers a notification of, or an application for, a variation in advance of the data submission date in accordance with this paragraph, the references in paragraphs 11(2)(c), (3)(c) and (5)(c)(ii) and 12(2)(c) to the data submission date are to be read as references to the date on which—

(a) the notification of, or the application for, the variation is submitted to the licensing authority in accordance with sub-paragraph (1); or

(b) the licensing authority notifies the holder that it will consider the notification or application, in accordance with sub-paragraph (2), without the information referred to in sub-paragraph (2)(b).

Applications for renewals of converted EU marketing authorisations made before exit day

14.—(1) This paragraph applies where a holder of a converted EU marketing authorisation has, before exit day, made an application to the EMA for renewal of the EU marketing authorisation in accordance with Article 14 of Regulation (EC) No 726/2004 but no final decision has been made in relation to that application by the European Commission before exit day.

(2) Where this paragraph applies—

(a) the holder of the converted EU marketing authorisation must (subject to paragraph 18) submit the application for renewal to the licensing authority with the baseline data; and

(b) the licensing authority must—

(i) where before exit day the Committee for Medicinal Products for Human Use has given a positive final opinion in relation to the application with which the United Kingdom concurred, treat the renewal application as accepted for the purposes of regulation 66 (application for renewal of authorisation), or

(ii) where before exit day the Committee for Medicinal Products for Human Use has not given any opinion or has given a negative final opinion in relation to the application, or where a positive final opinion has been given but the United Kingdom recorded a divergent opinion, treat the application as an application made in relation to the converted EU marketing authorisation under regulation 66 and consider the application in accordance with that regulation.

Applications for renewals of conditional marketing authorisations made before exit day

15.—(1) This paragraph applies where before exit day—

(a) a holder of a converted EU marketing authorisation which was granted as a conditional marketing authorisation within the meaning of Article 1 of Regulation (EC) No 507/2006 has made an application to the EMA for renewal of the authorisation in accordance with Article 6 of that Regulation; but

(b) no final decision has been made in relation to that application by the European Commission.

(2) Where this paragraph applies—

(a) the holder of the converted EU marketing authorisation must (subject to paragraph 18) submit the application for renewal to the licensing authority with the baseline data; and

(b) the licensing authority must—

(i) where before exit day the Committee for Medicinal Products for Human use has given a positive final opinion in relation to the application with which the United Kingdom concurred, treat the renewal application as accepted for the purposes of regulation 66B, or

(ii) where before exit day the Committee for Medicinal Products for Human Use has not given any opinion or has given a negative final opinion in relation to the application, or where a positive final opinion has been given but the United Kingdom recorded a divergent opinion, treat the application as an application made in relation to the converted EU marketing authorisation under regulation 66B (renewal of conditional marketing authorisation) and consider the application in accordance with that regulation.

Applications for renewals of converted EU marketing authorisations made after exit day

16.—(1) This paragraph applies where a holder of a converted EU marketing authorisation is due to make an application for renewal of the authorisation in accordance with regulation 66 (application for renewal of authorisation) during the period of one year beginning with exit day.

(2) Where this paragraph applies—

(a) the holder of the converted EU marketing authorisation must (subject to paragraph 18) submit the baseline data so that it is received by the licensing authority at the same time as the application for renewal is made;

(b) the licensing authority must consider the renewal application in accordance with regulation 66; and

(c) the converted EU marketing authorisation remains in force until the licensing authority notifies the holder of its decision on the renewal application.

Applications for renewals of conditional marketing authorisations made after exit day

17.—(1) This paragraph applies where the holder of a converted EU marketing authorisation which was granted as a conditional marketing authorisation within the meaning of Article 1 of Regulation (EC) No 507/2006 is due to make an application for renewal of the authorisation in accordance with regulation 66B during the period beginning with exit day and ending on the data submission date.

(2) Where this paragraph applies—

(a) the holder of the converted EU marketing authorisation must (subject to paragraph 18) submit the baseline data so that it is received by the licensing authority at the same time as the application for renewal is made;

(b) the licensing authority must consider the renewal application in accordance with regulation 66B (renewal of conditional marketing authorisation); and

(c) the authorisation remains in force until the licensing authority notifies the holder of its decision on the renewal application.

Renewals of converted EU marketing authorisations sought in advance of the data submission date

18.—(1) If a holder of a converted EU marketing authorisation submits an application for renewal in accordance with regulation 66 or 66B before the data submission date, it must, unless

sub-paragraph (2) applies, provide to the licensing authority with the application such information concerning the product to which the converted EU marketing authorisation relates as may be specified in writing by the licensing authority for this purpose and published on or before exit day.

(2) If a holder of a converted EU marketing authorisation wishes the licensing authority to consider a renewal application before the data submission date but does not provide the information described in sub-paragraph (1) with the application, the licensing authority may agree to consider the application if it is satisfied that—

(a) the renewal may be necessary on urgent safety grounds;

(b) the renewal may be necessary in order to maintain supplies of a particular medicinal product to patients in the United Kingdom; or

(c) there are other good reasons for considering the renewal in advance of the data submission date.

Article 61(3) notifications made before exit day in relation to converted EU marketing authorisations

19.—(1) This paragraph applies where, before exit day—

(a) a holder of a converted EU marketing authorisation has, in accordance with Article 61(3) of the 2001 Directive, notified the EMA of a proposed change to an aspect of the labelling or the package leaflet of the EU marketing authorisation to which the converted EU marketing authorisation relates; but

(b) the period of 90 days referred to in Article 61(3) has not elapsed and the EMA has not objected to the proposed change.

(2) Where this paragraph applies, and where the holder wishes the proposed change to apply in relation to the converted EU marketing authorisation—

(a) the holder may put the change into effect in relation to the converted EU marketing authorisation at the same time as it may be put into effect in relation to the EU marketing authorisation;

(b) the holder must (subject to paragraph 21) include with the baseline data—

(i) a copy of the notification, and

(ii) an indication of whether the EMA has opposed the proposed change; and

(c) the proposed change to the labelling or the package leaflet of the converted EU marketing authorisation is deemed to be accepted unless the licensing authority notifies the holder in writing within the period of 30 days beginning with the data submission date that the proposed change is opposed, in which case the holder must cease to apply the opposed change immediately after receipt of the notification.

Article 61(3) notifications made in relation to converted EU marketing authorisations after exit day but before the data submission date

20.—(1) This paragraph applies where, during the period beginning with exit day and ending on the day before the data submission date, a holder of a converted EU marketing authorisation notifies the EMA in accordance with Article 61(3) of the 2001 Directive of a proposed change to an aspect of the labelling or the package leaflet of the EU marketing authorisation to which the converted EU marketing authorisation relates.

(2) Where this paragraph applies, and where the holder wishes the proposed change to apply in relation to the converted EU marketing authorisation—

(a) the holder of the converted EU marketing authorisation may put the change into effect at the same time as it may be put into effect in relation to the EU marketing authorisation;

(b) the holder must (subject to paragraph 21) include with the baseline data—

(i) a copy of the notification, and

(ii) an indication of whether the EMA has opposed the proposed change; and

(c) the proposed change to the labelling or the package leaflet of the converted EU marketing authorisation is deemed to be accepted unless the licensing authority notifies the holder in writing within the period of 30 days beginning with the data submission date that the proposed change is opposed, in which case the holder must cease to apply the opposed change immediately after receipt of the notification.

Article 61(3) notifications sought in advance of the data submission date

21.—(1) If a holder of a converted EU marketing authorisation wishes to notify the licensing authority of a proposed change to an aspect of the labelling or the package leaflet of the EU marketing authorisation to which the converted EU marketing authorisation relates in advance of the data submission date, the holder must—

(a) submit the notification of the proposed change to the licensing authority; and

(b) unless sub-paragraph (2) applies, at the same time provide the licensing authority with such information concerning the product to which the converted EU marketing authorisation relates as may be specified in writing by the licensing authority for this purpose and published on or before exit day.

(2) If a holder of a converted EU marketing authorisation wishes the licensing authority to consider a proposed change before the data submission date but does not provide the information described in sub-paragraph (1)(b) with the notification, the licensing authority may agree to consider the notification if it is satisfied that—

(a) the proposed change may be necessary on urgent safety grounds;

(b) the proposed change may be necessary in order to maintain supplies of a particular medicinal product to patients in the United Kingdom; or

(c) there are other good reasons for considering the proposed change in advance of the data submission date.

(3) Where the licensing authority considers a proposed change in accordance with this paragraph, the references in paragraph 19(2)(c) and 20(2)(c) to the data submission date are to be read as references to the date on which—

(a) the proposed change is notified to the licensing authority in accordance with sub-paragraph (1); or

(b) the licensing authority notifies the holder that it will consider the notification, in accordance with sub-paragraph (2), without the information referred to in sub-paragraph (1)(b).

Place of establishment for converted EU marketing authorisation holder established in EEA state before exit day

22.—(1) Subject to sub-paragraph (2), a person who—

(a) holds a converted EU marketing authorisation on exit day (whether or not it is suspended); and

(b) was, immediately before exit day, established in an EEA State, and remains established there on and after exit day,

is to be treated, for the transitional period, as satisfying the requirements of regulation 49(3) or 66(2) (as the case may be), notwithstanding the amendments made to those provisions by the EU Exit Regulations.

(2) But sub-paragraph (1) continues to apply to a person after the end of the specified period only if the person has, before the end of that period, notified the licensing authority in writing of—

(a) a named individual who resides and operates in the United Kingdom who the licensing authority may contact in respect of any matter relating to the converted EU marketing authorisation during the transitional period; and

(b) that individual's address, telephone number and email address.

(3) In this paragraph—

"the specified period" means 4 weeks beginning with exit day; and

"the transitional period" means the period of 21 months beginning with exit day.

Temporary exemption as to packaging requirements for converted EU marketing authorisations

23.—(1) A holder of a converted EU marketing authorisation does not commit an offence under regulation 268 during the period of 33 months beginning with exit day to the extent that—

(a) the packaging and package leaflet do not comply with the requirements of Part 13 by reason only of the fact that the outer or immediate packaging, or the package leaflet, do not include the correct information as to—

(i) the name and address of the holder of the UK marketing authorisation, or, where applicable, the name of the holder's representative,

(ii) the number of the UK marketing authorisation, or

(iii) the name and address of the manufacturer of the product; and

(b) the outer and immediate packaging, or the package leaflet, do not include the correct information specified in paragraph (a)(i) to (iii) solely because—

(i) the number of the marketing authorisation is the number of the EU marketing authorisation to which the converted EU marketing authorisation relates, or

(ii) the UK marketing authorisation holder has established itself in the United Kingdom before the end of the period of 21 months beginning with exit day in order to comply with regulation 49(3), and the information specified in paragraph (a)(i) or (iii) is no longer correct as a consequence of that establishment in the United Kingdom.

(2) Sub-paragraph (1) only applies if—

(a) the packaging and package leaflet met the requirements of Part 13 as to the matters specified in sub-paragraph (1)(a)(i) to (iii) immediately before exit day; and

(b) the holder of the converted EU marketing authorisation, having been notified of the number of the UK marketing authorisation and having established itself in the United Kingdom, does not otherwise need to make any changes to the outer or immediate packaging, or the package leaflet, during the period referred to in sub-paragraph (1).

Referrals made under Article 20 of Regulation (EC) No 726/2004 that have not concluded or been implemented before exit day

24.—(1) Sub-paragraph (2) applies where—

(a) the European Commission has requested the opinion of the EMA in accordance with Article 20(2) of Regulation (EC) No 726/2004 in relation to a specified matter; but

(b) no final decision has been adopted by the European Commission in accordance with Article 20(3) of that Regulation immediately before exit day.

(2) Where this sub-paragraph applies, the licensing authority must make a decision in respect of the specified matter in accordance with regulation 68 (revocation, variation and suspension of UK marketing authorisation) as soon as reasonably practicable.

(3) In making a decision under regulation 68 in accordance with sub-paragraph (2), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the specified matter as a consequence of its involvement in the procedure under Article 20 of Regulation (EC) No 726/2004;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a member State in the making of that decision or agreement, under any procedure provided for in the Council Decision of 28 June 1999 laying down the procedure for the exercise of implementing powers conferred on the Commission; and

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11.

(4) Sub-paragraph (5) applies if the licensing authority is making a decision under regulation 68 in accordance with sub-paragraph (2) in a case where the Committee for Medicinal Products for Human Use has given a final opinion in relation to the specified matter.

(5) Where this sub-paragraph applies, the licensing authority may treat the opinion as if it were the opinion of the appropriate committee for the purposes of paragraph 5 of Schedule 11.

(6) Sub-paragraph (7) applies where—

(a) the European Commission has requested the opinion of the EMA in accordance with Article 20(2) of Regulation (EC) No 726/2004 in relation to a specified matter;

(b) a final decision has been adopted by the European Commission in accordance with Article 20(3) of that Regulation immediately before exit day; but

(c) the necessary steps to give effect to the decision referred to in paragraph (b) have not been taken before exit day.

(7) Where this sub-paragraph applies, the licensing authority must, where a Commission decision or opinion requires steps to be taken in respect of an EU marketing authorisation that is a converted EU marketing authorisation, take the steps necessary as a result of the decision or opinion to suspend, revoke or vary a converted EU marketing authorisation as soon as reasonably practicable.

(8) In this paragraph, "specified matter" means a matter in relation to which the opinion of the EMA has been requested by the European Commission under Article 20(2) of Regulation (EC) No 726/2004 before exit day that might result in the suspension, revocation or variation of an EU marketing authorisation which is a converted EU marketing authorisation.

Enforcement

25. If a holder of a converted EU marketing authorisation fails to comply with an obligation imposed on the holder by or under this Part, the licensing authority may suspend the authorisation until the holder complies with the obligation.

PART 4

Transitional provision in respect of UK marketing authorisations, parallel import licences and parallel distribution notices

Place of establishment for UK marketing authorisation holder or parallel import licence holder established in an EEA State before exit day

26.—(1) Subject to sub-paragraphs (2) and (3), any person—

(a) who—

(i) holds a UK marketing authorisation immediately before exit day which remains in force on exit day (whether or not it is suspended),

(ii) holds a parallel import licence immediately before exit day which remains in force on exit day (whether or not it is suspended),

(iii) has made an application for, or to renew, a UK marketing authorisation or parallel import licence before exit day, which has not been determined before that date, or

(iv) makes such an application on or after exit day but before the end of the transitional period; and

(b) who was, immediately before exit day, established in an EEA State and remains established there on and after exit day,

is to be treated, for the transitional period, as satisfying the requirements of regulation 49(3), 66(2) or 66A(2) (as the case may be), notwithstanding the amendments made to those provisions by the EU Exit Regulations.

(2) But sub-paragraph (1) continues to apply to a person only if the person has notified the licensing authority in writing of—

(a) a named individual who resides and operates in the United Kingdom who the licensing authority may contact in respect of any matter relating to the UK marketing authorisation or parallel import licence, or application for a UK marketing authorisation or parallel import licence (as the case may be), during the transitional period; and

(b) that individual's address, telephone number and email address.

(3) A person must notify the licensing authority under sub-paragraph (2)—

(a) where sub-paragraph (1)(a)(i) to (iii) applies, within the period of 4 weeks beginning with exit day; or

(b) where sub-paragraph (1)(a)(iv) applies, at the time of making the application.

(3) This paragraph does not apply to a UK marketing authorisation that is a converted EU marketing authorisation within the meaning of paragraph 6.

(4) In this paragraph "the transitional period" means the period of 21 months beginning with exit day.

Temporary exemption as to packaging requirements: change of place of establishment

27.—(1) Subject to sub-paragraph (2), a person to whom paragraph 26 applies does not commit an offence under regulation 268 (offence relating to packaging and package leaflets: holder of authorisation etc) during the transitional period to the extent that—

(a) the packaging and package leaflet do not comply with the requirements of Part 13 (packaging and leaflets) by reason only of the fact that the outer or immediate

packaging, or the package leaflet (as the case may be), do not include the correct information as to—

(i) the name and address of the holder of the UK marketing authorisation, or, where applicable, the name of that holder's representative,

(ii) the number of the UK marketing authorisation, or

(iii) the name and address of the manufacturer of the product; and

(b) the outer and immediate packaging, or the package leaflet, do not include the correct information specified in paragraph (a)(i) to (iii) solely because—

(i) the UK marketing authorisation holder has established itself in the United Kingdom before the end of the period of 21 months beginning with exit day in order to comply with regulation 49(3), and

(ii) the information specified in paragraph (a)(i) to (iii) is no longer correct as a consequence of that establishment in the United Kingdom.

(2) Sub-paragraph (1) only applies if—

(a) the packaging and package leaflet met the requirements of Part 13 as to the matters specified in paragraph (1)(a)(i) to (iii) immediately before exit day; and

(b) the UK marketing authorisation holder, having established itself in the United Kingdom, does not otherwise need to make any changes to the outer or immediate packaging, or the package leaflet, as the case may be, during the transitional period.

(3) In this paragraph "the transitional period" means the period of 33 months beginning with exit day.

Conversion of parallel distribution notices in to parallel import licences

28.—(1) Sub-paragraph (2) applies where—

(a) a person holds a parallel distribution notice, issued by the EMA, for a medicinal product in respect of which there is an EU marketing authorisation;

(b) that distribution notice, and that EU marketing authorisation, are in force immediately before exit day; and

(c) that parallel distribution notice specifies the United Kingdom as a member state of destination in respect of that medicinal product.

(2) Subject to sub-paragraph (3), a person who falls within sub-paragraph (1) is deemed, on and after exit day, to have a parallel import licence granted under Part 5 in respect of the medicinal product specified in the parallel distribution notice.

(3) A person who falls within sub-paragraph (1) continues to hold a parallel import licence pursuant to sub-paragraph (2) only if that person notifies the licensing authority—

(a) before the end of the period of 21 days beginning with exit day, of each medicinal product, and each country from which it is intended to import that product on or after exit day; and

(b) of any other information that the licensing authority requests, within such time period as the licensing authority may specify.

(4) The licensing authority must as soon as reasonably practicable after receipt of the information specified in sub-paragraph (3), issue a parallel import licence to the holder of the parallel distribution notice.

Inclusion of the batch testing condition in relevant UK marketing authorisations, and batch testing of biological medicinal products in the EEA before exit day (regulation 60A)

29.—(1) Sub-paragraph (2) applies where—

(a) a marketing authorisation was in force before exit day,

(b) that authorisation is in force as a UK marketing authorisation on exit day (whether or not it is suspended); and

(c) that authorisation is for a medicinal product of a type that is specified in regulation 60A(2)(a) to (e) (condition as to the submitting of samples and other information to the appropriate authority).

(2) Where this sub-paragraph applies, the UK marketing authorisation is deemed to include the batch testing condition on and after exit day.

(3) Sub-paragraph (4) applies where a holder of a UK marketing authorisation has, before exit day, submitted to a competent authority of an EEA State samples for testing from a batch of a medicinal product ("the relevant batch") that—

(a) is the subject of that authorisation; and

(b) is of a type specified in regulation 60A(2)(a) to (e).

(4) Where this sub-paragraph applies, the holder of the UK marketing authorisation is deemed to have satisfied the batch testing condition in respect of the relevant batch if, before exit day—

(a) the competent authority of that EEA State examines the sample from the relevant batch; and

(b) that authority declared it to be in conformity with the approved specifications (within the meaning of Article 114 of the 2001 Directive) before exit day.

(5) The appropriate authority—

(a) must include each EEA State on the list it publishes under regulation 60A(5) on exit day; and

(b) must not, before the end of the transitional period, exercise its powers under regulation 60A(8) to remove an EEA State from the list it publishes under regulation 60A(5).

(6) For the purposes of regulation 60A(9), the appropriate authority must, on exit day—

(a) include Switzerland and Israel in the list it publishes under that paragraph; and

(b) include in respect of those countries any conditions or restrictions in the arrangement with those countries that affect the applicability of the batch testing exemption.

(7) In this paragraph—

(a) "the transitional period" means the period of 21 months beginning with exit day; and

(b) "the batch testing condition" and "the batch testing exemption" have the same meaning as in regulation 60A.

Existing data and marketing exclusivity and global marketing authorisations

30.—(1) Sub-paragraph (2) applies in relation to a UK marketing authorisation which, immediately before exit day, is part of a global marketing authorisation with one or more EU marketing authorisations or marketing authorisations granted by the competent authority of an EEA state.

(2) Where this sub-paragraph applies, the provisions of regulation 48(5) (definitions for Part 5), in so far as they describe a global marketing authorisation by reference to UK marketing

authorisations only, do not affect the periods of data and marketing exclusivity to which the holder of a UK marketing authorisation to which this paragraph applies is entitled immediately before exit day.

Applications for EU marketing authorisations made before exit day

31.—(1) Sub-paragraph (2) applies where, before exit day—

(a) an application has been made to the EMA for an EU marketing authorisation; but

(b) no final decision has been made by the European Commission in relation to the grant of an EU marketing authorisation under Article 10 of Regulation (EC) No 726/2004.

(2) Where this sub-paragraph applies, the applicant may apply to the licensing authority for the grant of a UK marketing authorisation by submitting to the licensing authority—

(a) a copy of the application for the EU marketing authorisation; and

(b) if requested by the licensing authority, such material or information that the licensing authority reasonably considers necessary for dealing with the application.

(3) Sub-paragraph (4) applies where, before exit day and in relation to an application to which sub-paragraph (2) applies, a final opinion favourable to the granting of an EU marketing authorisation has been given by the Committee for Medicinal Products for Human Use and the United Kingdom concurred with that opinion.

(4) Where this sub-paragraph applies, the licensing authority must grant a UK marketing authorisation in response to an application as described in sub-paragraph (2) as soon as reasonably practicable after it is received.

(5) Sub-paragraph (6) applies where before exit day, in relation to an application to which sub-paragraph (2) applies—

(a) no final opinion favourable to the granting of an EU marketing authorisation has been given by the Committee for Medicinal Products for Human Use; or

(b) such an opinion has been given but the United Kingdom recorded a divergent opinion.

(6) Where this sub-paragraph applies, the licensing authority must consider an application made under sub-paragraph (2) in accordance with Part 5 of these Regulations (marketing authorisations).

Place of establishment for UK marketing authorisation holder established in EEA state before exit day (pre-exit EU marketing authorisation applications)

32.—(1) Subject to sub-paragraph (2), a person—

(a) who applied to the EMA for an EU marketing authorisation before exit day;

(b) to whom the licensing authority grants a UK marketing authorisation on or after exit day in response to that application in accordance with paragraph 31; and

(c) who was, immediately before exit day, established in an EEA State, and remains established there on and after exit day,

is to be treated, for the transitional period, as satisfying the requirements of regulation 49(3), notwithstanding the amendments made to those provisions by the EU Exit Regulations.

(2) Sub-paragraph (1) applies to a person only if, when submitting a copy of the application for the EU marketing authorisation to the licensing authority in accordance with paragraph 31, the person notifies the licensing authority in writing of—

(a) a named individual who resides and operates in the United Kingdom whom the licensing authority may contact in respect of any matter relating to the UK marketing authorisation during the transitional period; and

(b) that individual's address, telephone number and email address.

(3) In this paragraph, "the transitional period" means the period which beginning with the date on which the licensing authority grants a UK marketing authorisation as described in paragraph 31(4) and ending 21 months after exit day.

Packaging in relation to UK marketing authorisations granted in response to application for EU marketing authorisation made before exit day

33.—(1) Subject to sub-paragraph (2), a person to whom paragraph 32(1) applies does not commit an offence under regulation 268 (offence relating to packaging and package leaflets: holder of authorisation etc) during the transitional period to the extent that—

(a) the packaging and package leaflet do not comply with the requirements of Part 13 (packaging and leaflets) by reason only of the fact that the outer or immediate packaging, or the package leaflet, do not include the correct information as to—

(i) the name and address of the holder of the marketing authorisation, or, where applicable, the name of the holder's representative,

(ii) the number of the marketing authorisation, or

(iii) the name and address of the manufacturer of the product; and

(b) the outer and immediate packaging, or the package leaflet, do not include the correct information specified in paragraph (a)(i) to (iii) solely because—

(i) the number of the marketing authorisation is the number of the EU marketing authorisation to which the application for the EU marketing authorisation related, or

(ii) the UK marketing authorisation holder has established itself in the United Kingdom before the end of the period of 21 months beginning with exit day in order to comply with regulation 49(3), and the information specified in paragraph (a)(i) or (iii) is no longer correct as a consequence of that establishment in the United Kingdom.

(2) Sub-paragraph (1) only applies if—

(a) the packaging and package leaflet met the requirements of Part 13 as to the matters specified in sub-paragraph (1)(a)(i) to (iii) immediately before exit day; and

(b) the UK marketing authorisation holder, being aware of the number of the UK marketing authorisation and having established in the United Kingdom, does not otherwise need to make any changes to the outer or immediate packaging, or the package leaflet, as the case may be, during the transitional period.

(3) In this paragraph, "the transitional period" means the period beginning with the date on which the licensing authority grants a UK marketing authorisation as described in paragraph 31(4) and ending 33 months after exit day.

Applications made for a UK marketing authorisation before exit day to which Chapter 4 of Title III of the 2001 Directive applied

34.—(1) Sub-paragraph (2) applies where an application for a UK marketing authorisation has been made before exit day and—

(a) regulation 58(6) and (7) of the 2012 Regulations (applications to be determined under Chapter 4 of Title III of the 2001 Directive) applied to that application before exit day; but

(b) a decision as specified in Article 28(5) of the 2001 Directive has not been adopted by the licensing authority before exit day.

(2) Where this sub-paragraph applies, the licensing authority must—

(a) where the procedure specified in Article 28(4) of the 2001 Directive has concluded before exit day in relation to that application, grant a UK marketing authorisation in respect of that application as soon as reasonably practicable, and in any event before the end of the period of 30 days, beginning with exit day; or

(b) where the procedure specified in Article 28(4) of the 2001 Directive has not concluded before exit day, determine that application in accordance with Part 5 of these Regulations (marketing authorisations) as soon as reasonably practicable, unless the applicant notifies the licensing authority in writing that they no longer want the application to proceed.

(3) In making a determination under sub-paragraph (2)(b), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the application as a consequence of its involvement in any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a reference member state or concerned member state in the making of that decision or agreement, under any procedure provided for in Chapter 4 of Title III of the 2001 Directive; and

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11 (advice and representations).

(3) In making a determination under sub-paragraph (2)(b), the licensing authority must take all reasonable steps to ensure that it makes a decision to grant or refuse a UK marketing authorisation in the time period specified in regulation 58(1) (consideration of application) as if it had applied to that application on the date on which the application was submitted.

Transitional provision in respect of Plasma Master Files

35.—(1) This paragraph applies in relation to a UK marketing authorisation or EU marketing authorisation—

(a) which was granted before exit day;

(b) the application for which made reference to a Plasma Master File within the meaning of paragraph 1.1(a), first indent, of Part III of Annex I to the 2001 Directive which was certified by the EMA in accordance with paragraph 1.1(c) of that Part of the Annex; and

(c) which remains in force as a UK marketing authorisation on and after exit day.

(2) A holder of the UK marketing authorisation to which this paragraph applies may, subject to complying with the obligations in sub-paragraph (3), continue to refer to the Plasma Master File as certified by the EMA, notwithstanding the modifications to paragraph 1.1(c) of Part III of Annex I to the 2001 Directive in Schedule 8B, subject which that paragraph is to be read on and after exit day.

(3) The holder of a UK marketing authorisation to which this paragraph applies must notify the licensing authority of—

(a) the outcome of the annual update and recertification of the Plasma Master File by the EMA within 4 weeks beginning with the completion of that update and recertification;

(b) any application for changes to the terms of the Plasma Master File which the holder seeks from the EMA, within 4 weeks beginning with the date of the application; and

(c) the outcome of any application referred to in paragraph (b), within 4 weeks beginning with the date on which the holder is notified of that outcome.

(4) The licensing authority may at any time review the terms of a Plasma Master File to which reference is made in accordance with sub-paragraph (2), with a view to exercising its powers under these Regulations in relation to the UK marketing authorisation.

Suspensions of UK marketing authorisations that have effect immediately before exit day that were imposed under Chapter 4 of Title III of the 2001 Directive or Regulation (EC) No 726/2004

36. Where, immediately before exit day, a marketing authorisation, which is a UK marketing authorisation on exit day, has been suspended pursuant to the procedures in Chapter IV of Title III of 2001 Directive or Regulation (EC) No 726/2004, the suspension—

(a) continues to have effect on and after exit day in accordance with the terms on which it was imposed; and

(b) is to be treated as if it had been imposed by the licensing authority under Part 5 (marketing authorisations).

Referrals made under Article 31 of the 2001 Directive concerning the suspension, variation or revocation of an EU marketing authorisation or a UK marketing authorisation that have not concluded before exit day

37.—(1) Sub-paragraph (2) applies where—

(a) a specified matter has been referred under Article 31 of the 2001 Directive before exit day; but

(b) that procedure has not concluded before exit day.

(2) Where this sub-paragraph applies, the licensing authority must make a decision in respect of the specified matter in accordance with regulation 68 (revocation, variation and suspension of UK marketing authorisation) as soon as reasonably practicable.

(3) In making a decision under regulation 68 in accordance with sub-paragraph (2), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the specified matter as a consequence of its involvement in any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a member state in the making of that decision or agreement, under any procedure provided for in Chapter 4 of Title III of the 2001 Directive; and

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11.

(4) Sub-paragraph (5) applies if the licensing authority is making a decision under regulation 68 in accordance with sub-paragraph (2) in a case where the Committee for Medicinal Products for Human Use or the Co-ordination Group for Mutual Recognition and Decentralised Procedures (as the case may be) has given a final opinion in relation to the matter referred under Article 31 of the 2001 Directive.

(5) Where this sub-paragraph applies, the licensing authority may treat the opinion as if it were the opinion of the appropriate committee for the purposes of paragraph 5 of Schedule 11 (advice and representations).

(6) Sub-paragraph (7) applies where—

(a) a specified matter has been referred under Article 31 of the 2001 Directive before exit day;

(b) that referral has concluded before exit day; but

(c) the licensing authority has not, before exit day, taken the steps necessary to give effect to that decision or that opinion (as the case may be).

(7) Where this sub-paragraph applies, the licensing authority must take the steps necessary as a result of the decision or opinion to suspend, revoke or vary the UK marketing authorisation—

(a) as soon as reasonably practicable; and

(b) in the case of a UK marketing authorisation that is not a converted EU marketing authorisation, within the period specified in Article 34(3) of the 2001 Directive (if relevant).

(8) In this paragraph—

"concluded before exit day", in relation to an Article 31 referral, means—

(a) a Commission decision as provided for in Article 34(3) of the 2001 Directive has been taken before exit day; or

(b) an opinion of the Co-ordination Group for Mutual Recognition and Decentralised Procedures, which constituted the end of the Article 31 referral procedure, has been given before exit day; and

"specified matter" means—

(a) a matter referred under Article 31 of the 2001 Directive before exit day that concerns a proposal to suspend, revoke or otherwise vary a UK marketing authorisation or an EU marketing authorisation; but

(b) does not include a referral made under Article 107i of the 2001 Directive.

PART 5

Transitional provision in relation to variations of marketing authorisations other than converted EU marketing authorisations

Application or notification made before exit day in respect of a variation under Chapter IIa of Regulation (EC) No 1234/2008 (variations to purely national marketing authorisations)

38.—(1) Sub-paragraph (2) applies where—

(a) an application or notification in respect of a variation to a UK marketing authorisation has been submitted to the licensing authority under Chapter IIa of Regulation (EC) No 1234/2008 before exit day; but

(b) the procedures specified in Article 13e of that Regulation (measures to close the variation procedures in Chapter IIa of that Regulation) have not concluded before exit day.

(2) Where this sub-paragraph applies, the licensing authority must—

(a) determine which of the provisions specified in Schedule 10A that are relevant to that application or notification need to be taken on or after exit day, having regard to the steps that have already been undertaken under Chapter IIa of Regulation (EC) No 1234/2008 before exit day;

(b) assess the application or notification in accordance with the provisions of that Schedule the authority has determined are relevant to the application, as if the application or notification had been made under them; and

(c) take all reasonable steps to ensure that it assesses the notification or application in accordance with any relevant time period specified in that Schedule, as if the application had been made under the provisions in that Schedule before exit day.

(3) Paragraphs 15 and 16 of Schedule 10A apply to any variation that falls under sub-paragraph (1)(a) or (b).

Application or notification made before exit day in respect of a variation under Chapter II of Regulation (EC) No 1234/2008 (variations to marketing authorisations granted in accordance with Chapter 4 of the 2001 Directive)

39.—(1) This paragraph applies where an application or notification in respect of a variation to a marketing authorisation has been submitted to the licensing authority, as a relevant authority, under Chapter II of Regulation (EC) No 1234/2008 before exit day.

(2) If the procedures specified in Article 11(1) of Regulation (EC) No 1234/2008 have not concluded before exit day, the licensing authority must—

(a) assess the application or notification in accordance with regulation 65C and Schedule 10A to these Regulations, as if the application or notification had been made under those provisions; and

(b) make such an assessment having regard to the matters specified in sub-paragraph (5).

(3) If the procedures specified in Article 11(1) of Regulation (EC) No 1234/2008 have concluded before exit day—

(a) the licensing authority must take the steps specified in Article 11(2) of Regulation (EC) No 1234/2008 within the time limit specified in Article 23(1) of that Regulation; and

(b) paragraphs 15 and 16 of Schedule 10A apply to the variation.

(4) In making a determination under sub-paragraph (2), the licensing authority must—

(a) determine which steps of the procedures specified in Schedule 10A that are relevant to that application or notification need to be taken on or after exit day, having regard to the matters specified in sub-paragraph (5); and

(b) take all reasonable steps to ensure that it assesses the notification or application in accordance with any time period specified in that Schedule, as if the application had been made under the provisions in that Schedule before exit day.

(5) In making a determination under sub-paragraph (2), the licensing authority must have regard to—

(a) any recommendation in relation to that application or notification given before exit day pursuant to Article 5 of Regulation (EC) No 1234/2008;

(b) any relevant information obtained by it before exit day, as a relevant authority, in relation to the application or notification by virtue of any procedure provided for in Chapter II of that Regulation; and

(c) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a relevant authority, including any matter referred under the procedure specified in Article 13 of that Regulation.

Application or notification in respect of a variations made before exit day under Article 20 of Regulation (EC) No 1234/2008 (work-sharing procedure)

40.—(1) Sub-paragraph (2) applies where—

(a) an application or notification in respect of a variation to a UK marketing authorisation has been submitted to the licensing authority, as a relevant authority or the reference authority, under Article 20 of Regulation (EC) No 1234/2008;

(b) the marketing authorisation is one to which Chapter II or IIa of that Regulation applied; and

(c) the procedure in Article 20(8) has not been completed before exit day.

(2) Where this sub-paragraph applies, the licensing authority must—

(a) determine which of the provisions specified in Schedule 10A that are relevant to that application or notification need to be taken on or after exit day, having regard to the steps that have already been undertaken under Article 20 of Regulation (EC) No 1234/2008 before exit day;

(b) assess the application or notification in accordance with the relevant provisions in that Schedule, as if the application or notification had been made under them; and

(c) take all reasonable steps to ensure that it assesses the notification or application in accordance with any relevant time period specified in that Schedule, as if the application had been made under the provisions in that Schedule before exit day.

(3) In making a determination or assessment under sub-paragraph (2), the licensing authority must have regard to—

(a) any opinion given by the reference authority before exit day in relation to that application;

(b) any relevant information obtained by it before exit day, as a reference authority or relevant authority, in relation to the application or notification by virtue of any procedure provided for in regulation 20 of Regulation (EC) No 1234/2008; and

(c) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a relevant authority.

(4) Paragraphs 15 and 16 of Schedule 10A apply to any variation that falls under sub-paragraph (1).

PART 6

Transitional provision in relation to the Paediatric Regulation

Transitional provision in relation to applications made to EMA before exit day under the Paediatric Regulation

41.—(1) Where a paediatric investigation plan has been agreed by the EMA in accordance with the Paediatric Regulation before exit day, that plan, including any modifications agreed by the EMA before exit day, has effect on and after exit day as an agreed paediatric investigation plan.

(2) Sub-paragraph (3) applies where—

(a) a paediatric investigation plan has been submitted to the EMA with a request for agreement before exit day;

(b) the proposed paediatric plan is valid in accordance with the provisions of Article 15(2) of the Paediatric Regulation; but

(c) the EMA has not adopted a decision to agree the plan before exit day.

(3) Where this sub-paragraph applies, the licensing authority must—

(a) where an opinion favourable to agreeing the paediatric investigation plan with which the United Kingdom concurred has been given by the Paediatric Committee before exit day, treat the plan as an agreed paediatric investigation plan;

(b) where an opinion against agreeing the paediatric investigation plan with which the United Kingdom concurred has been given by the Paediatric Committee before exit day, decide that it cannot agree the plan under regulation 50B(5) (agreement and modification of paediatric investigation plan); or

(c) where before exit day no opinion in relation to the paediatric investigation plan has been given by the Paediatric Committee, or where such an opinion has been given but the United Kingdom recorded a divergent opinion, treat it as a request for agreement under regulation 50B(1) and determine that request as soon as reasonably practicable, unless the applicant notifies the licensing authority in writing that they do not want the application to proceed as a request for agreement of a paediatric investigation plan under these Regulations.

(4) Sub-paragraph (5) applies where—

(a) a paediatric investigation plan has been agreed by the EMA in accordance with the Paediatric Regulation before exit day;

(b) the person to whom the EMA's decision to agree the plan was addressed has, before exit day, made a proposal under Article 22 of the Paediatric Regulation to modify the plan, or to request a waiver; but

(c) the EMA has not adopted a decision to agree to the modification or waiver before exit day.

(5) Where this sub-paragraph applies, the licensing authority must—

(a) where an opinion favourable to agreeing the modification or waiver with which the United Kingdom concurred has been given by the Paediatric Committee before exit day, agree to the modification or waiver as if it had been requested under regulation 50B(6);

(b) where an opinion against agreeing the modification or waiver with which the United Kingdom concurred has been given by the Paediatric Committee before exit day, decide that it cannot agree to the modification or waiver as if it had been requested under regulation 50B(6); or

(c) where before exit day no opinion in relation to the modification or waiver has been given by the Paediatric Committee, or where such an opinion has been given but the United Kingdom recorded a divergent opinion, treat the proposal as one made under regulation 50B(6) and consider it accordingly, unless the applicant notifies the licensing authority in writing that they do not want the proposal to proceed as a proposal under regulation 50B(6).

(6) Where the EMA has adopted a decision to grant, and has not revoked, a waiver of the obligation to produce the information in Article 7(1)(a) of the Paediatric Regulation before exit day, that waiver has effect on and after exit day as a waiver granted by the licensing authority under regulation 50D (waiver of production of information in a paediatric investigation plan).

(7) Sub-paragraph (8) applies where—

(a) an application has been made to the EMA for a waiver of the obligation to produce the information in Article 7(1)(a) of the Paediatric Regulation before exit day;

(b) the application has been accepted as valid by the EMA; but

(c) the EMA has not adopted a decision to grant the waiver before exit day.

(8) Where this sub-paragraph applies, the licensing authority must—

(a) where an opinion favourable to agreeing the waiver with which the United Kingdom concurred has been given by the Paediatric Committee before exit day, grant the waiver under regulation 50D(2);

(b) where an opinion against agreeing the waiver with which the United Kingdom concurred has been given by the Paediatric Committee before exit day, decide that it cannot grant the waiver under regulation 50D(2); or

(c) where before exit day no opinion in relation to the waiver has been given by the Paediatric Committee, or where such an opinion has been given but the United Kingdom recorded a divergent opinion, treat the proposal as one made under regulation 50D and consider it accordingly, unless the applicant notifies the licensing authority in writing that they do not want the proposal to proceed as a proposal under regulation 50D.

PART 7

Transitional provision in relation to orphan medicinal products

Transitional provision in relation to applications made to EMA before exit day for orphan medicinal products

42.—(1) This sub-paragraph applies where—

(a) before exit day—

(i) an application has been made to the EMA for an EU marketing authorisation in relation to a medicinal product which has been approved as an orphan medicinal product by the European Commission pursuant to Article 5 of the Orphan Regulation and which appears in the Orphan Register, but

(ii) no final decision has been made by the European Commission in relation to maintaining the product's inclusion in the Orphan Register following the grant of an EU marketing authorisation, and

(b) on or after exit day, the licensing authority is granting or considering an application for a UK marketing authorisation in relation to the product in accordance with paragraph 31(4) or (6).

(2) Where sub-paragraph (1) applies, the licensing authority must—

(a) where an opinion favourable to the maintenance of the inclusion of the medicinal product in the Orphan Register with which the United Kingdom concurred has been given by the COMP before exit day in relation to the application, decide for the purposes of regulation 58C(1)(a) (consideration of applications relating to orphan medicinal products) that the orphan criteria are met in relation to the product, or

(b) where no opinion favourable to such maintenance has been given by the COMP before exit day in relation to the application, or where such an opinion has been given but the United Kingdom recorded a divergent opinion, reach its own view for the purposes of regulation 58C(1)(a) as to whether the orphan criteria are met in relation to the product.

(3) In this paragraph, "Orphan Register" means the Community register of Orphan Medicinal Products as referred to in Article 5 of the Orphan Regulation.

PART 8

Transitional provision in respect of homoeopathic medicinal products

List of countries for the purposes of the definition of "homoeopathic medicinal product" on exit day

43.—(1) For the purposes of the definition of "homoeopathic medicinal product" in regulation 8 (general interpretation: accepted Pharmacopoeias for homoeopathic manufacturing procedures), during the transitional period, the licensing authority must publish a list of countries that includes each EEA State in it.

(2) The licensing authority must not, before the end of the transitional period, remove an EEA State from the list described in sub-paragraph (1).

(3) In this paragraph, "the transitional period" is the period of two years beginning with exit day.

Place of establishment for holders of certificates of registration established in EEA before exit day

44.—(1) Subject to sub-paragraph (2), any person—

(a) who—

(i) holds a certificate of registration immediately before exit day which remains in force on exit day (whether or not it is suspended),

(ii) has made an application for, or to renew, a certificate of registration before exit day, which has not been determined by the licensing authority before that date, or

(iii) makes such an application on or after exit day but before the end of the transitional period; and

(b) who was, immediately before exit day, established in an EEA State and who remains there on and after that day,

is to be treated, for the transitional period, as satisfying the requirements of regulation 103(4) or 108(2) (as the case may be), notwithstanding the amendments made to those provisions by the EU Exit Regulations.

(2) But sub-paragraph (1) continues to apply to a person only if the person has notified the licensing authority in writing of—

(a) a named individual who resides and operates in the United Kingdom who the licensing authority may contact in respect of any matter relating to the certificate of registration, or application for a certificate of registration, during the transitional period; and

(b) that individual's address, telephone number and email address.

(3) A person must notify the licensing authority under sub-paragraph (2)—

(a) where sub-paragraph (1)(a)(i) or (ii) applies, within the period of 4 weeks beginning with exit day; or

(b) where sub-paragraph (1)(a)(iii) applies, at the time of making the application.

(4) In this paragraph "the transitional period" means the period of 21 months beginning with exit day.

Temporary exemption as to packaging requirements: change of place of establishment

45.—(1) Subject to sub-paragraph (2), a person to whom paragraph 44 applies does not commit an offence under regulation 268 (offence relating to packaging and package leaflets) during the transitional period in relation to a product to the extent that—

(a) the packaging and package leaflet do not comply with the requirements of Part 13 (packaging and leaflets) by reason only of the fact that the outer or immediate packaging, or the package leaflet (as the case may be), do not include the correct information as to—

(i) the name and address of the holder of the certificate of registration,

(ii) the number of the certificate of registration, or

(iii) the name and address of the manufacturer of the product if different from the holder of the certificate of registration; and

(b) the outer and immediate packaging, or the package leaflet, do not include the correct information specified in paragraph (a)(i) to (iii) solely because—

(i) the holder of the certificate of registration has established itself in the United Kingdom before the end of the period of 21 months beginning with exit day in order to comply with regulation 103(4) or 108(2), and

(ii) the information specified in paragraph (a)(i) to (iii) is no longer correct as a consequence of that establishment in the United Kingdom.

(2) Sub-paragraph (1) only applies if—

(a) the packaging and package leaflet met the requirements of Part 13 as to the matters specified in sub-paragraph (1)(a)(i) to (iii) immediately before exit day; and

(b) the certificate of registration holder, having established itself in the United Kingdom, does not otherwise need to make any changes to the outer or immediate packaging, or the package leaflet, as the case may be, during the transitional period.

(3) In this paragraph "the transitional period" means the period of 33 months beginning with exit day.

Applications made for a certificate of registration for a registrable homoeopathic product before exit day to which Chapter 4 of Title III of the 2001 Directive applied

46.—(1) Sub-paragraph (2) applies where an application for a certificate of registration has been made before exit day and—

(a) regulation 104(5) and (6) (applications to be determined under Chapter 4 of Title III of the 2001 Directive) applied to that application before exit day; but

(b) a decision as specified in Article 28(5) of the 2001 Directive has not been adopted by the licensing authority before exit day.

(2) Where this sub-paragraph applies, the licensing authority must—

(a) where the procedure specified in Article 28(4) of the 2001 Directive has concluded before exit day in relation to that application, grant a certificate of registration in respect of that application as soon as reasonably practicable, and in any event before the end of the period of 30 days, beginning with exit day; or

(b) where the procedure specified in Article 28(4) of the 2001 Directive has not concluded before exit day, determine that application in accordance with Part 6 of these Regulations as soon as reasonably practicable, unless the applicant notifies the licensing authority in writing that they no longer want the application to proceed.

(3) In making a determination under sub-paragraph (2)(b), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the application as a consequence of its involvement in any procedure provided for in Chapter 4 of Title III of the 2001 Directive; and

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a reference member state or concerned member state in the making of that decision or agreement, under any procedure provided for in Chapter 4 of Title III of the 2001 Directive.

(4) In making a determination under sub-paragraph (2)(b), the licensing authority must take all reasonable steps to ensure that it makes a decision to grant or refuse a certificate of registration in the time period specified in regulation 104(1) as if it had applied to that application on the date on which the application was submitted.

Suspensions of certificates of registration that have effect immediately before exit day that were imposed under Chapter 4 of Title III of the 2001 Directive

47. Where, immediately before exit day, a certificate of registration has been suspended pursuant to the procedures in Chapter IV of Title III of 2001 Directive, the suspension—

(a) continues to have effect on and after exit day in accordance with the terms on which it was imposed; and

(b) is to be treated as if it had been imposed by the licensing authority under Part 6 of these Regulations (certification of homoeopathic medicinal products).

Referrals made under Article 31 of the 2001 Directive concerning the suspension, variation or revocation of a certificate of registration that have not concluded before exit day

48.—(1) Sub-paragraph (2) applies where—

(a) a specified matter has been referred under Article 31 of the 2001 Directive before exit day; but

(b) the procedure has not concluded before exit day.

(2) Where this sub-paragraph applies, the licensing authority must make a decision in respect of the specified matter in accordance with regulation 110 (revocation, variation and suspension of certificate of registration) as soon as reasonably practicable.

(3) In making a decision under regulation 110 in accordance with sub-paragraph (2), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the specified matter as a consequence of its involvement in any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a member state in the making of that decision or agreement, under any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11 (advice and representations).

(4) Sub-paragraph (5) applies if the licensing authority is making a decision under regulation 110 in accordance with sub-paragraph (2) in a case where the Co-ordination Group for Mutual Recognition and Decentralised procedures has given an opinion in relation to the matter under Article 31 of the Directive.

(5) Where this sub-paragraph applies, the licensing authority may treat the opinion as if it were the opinion of the appropriate committee for the purposes of paragraph 5 of Schedule 11.

(6) Sub-paragraph (7) applies where—

(a) a specified matter has been referred under Article 31 of the 2001 Directive before exit day;

(b) the referral has concluded before exit day; but

(c) the licensing authority has not, before exit day, taken the steps necessary to give effect to that decision or that opinion (as the case may be).

(7) The licensing authority must take the steps necessary as a result of the decision or opinion to suspend, revoke or vary the certificate of registration within the time period specified in Article 34(3) of the 2001 Directive where the decision or opinion requires steps to be taken in relation to a certificate of registration.

(8) In this paragraph—

"concluded before exit day", in relation to an Article 31 referral, means—

(a) a Commission decision as provided for in Article 34(3) of the 2001 Directive has been taken before exit day; or

(b) an opinion of the Co-ordination Group for Mutual Recognition and Decentralised Procedures, which constituted the end of the Article 31 referral procedure, has been given before exit day;

"specified matter" means—

(a) a matter referred under Article 31 of the 2001 Directive before exit day that concerns a proposal to suspend, revoke or otherwise vary a certificate of registration; but

(b) does not include a referral made under Article 107i of the 2001 Directive.

PART 9

Transitional provision in respect of traditional herbal registrations

Place of establishment for holders of traditional herbal registrations established in EEA before exit day

49.—(1) Subject to sub-paragraph (2), any person—

(a) who—

(i) holds a traditional herbal registration immediately before exit day which remains in force on exit day (whether or not it is suspended),

(ii) has made an application for, or to renew, a traditional herbal registration before exit day, which has not been determined by the licensing authority before that date, or

(iii) makes such an application on or after exit day but before the end of the transitional period; and

(b) who was, immediately before exit day, established in an EEA State and who remains there on and after that day,

is to be treated, for the transitional period, as satisfying the requirements of regulation 127(3) or 133(2) (as the case may be), notwithstanding the amendments made to those provisions by the EU Exit Regulations.

(2) But sub-paragraph (1) continues to apply to a person only if the person notifies the licensing authority in writing of—

(a) a named individual who resides and operates in the United Kingdom who the licensing authority may contact in respect of any matter relating to the traditional herbal registration, or application for a traditional herbal registration, during the transitional period; and

(b) that individual's address, telephone number and email address.

(3) A person must notify the licensing authority under sub-paragraph (2)—

(a) where sub-paragraph (1)(a)(i) or (ii) applies, within the period of 4 weeks beginning with exit day; or

(b) where sub-paragraph (1)(a)(iii) applies, at the time of making the application.

(4) In this paragraph "the transitional period" means the period of 21 months beginning with exit day.

Temporary exemption as to packaging requirements: change of place of establishment

50.—(1) Subject to sub-paragraph (2), a person to whom paragraph 49 applies does not commit an offence under regulation 268 (offence relating to packaging and package leaflets) during the transitional period in relation to a product to the extent that—

(a) the packaging and package leaflet do not comply with the requirements of Part 13 (packaging and leaflets) by reason only of the fact that the outer or immediate packaging, or the package leaflet (as the case may be), do not include the correct information as to—

(i) the name and address of the holder of the traditional herbal registration, or, if applicable, the holder's representative,

(ii) the number of the traditional herbal registration, or

(iii) the name and address of the manufacturer of the product; and

(b) the outer and immediate packaging, or the package leaflet, do not include the correct information specified in paragraph (a)(i) to (iii) solely because—

(i) the holder of the traditional herbal registration has established itself in the United Kingdom before the end of the period of 21 months beginning with exit day in order to comply with regulation 127(3) or 133(2), and

(ii) the information specified in paragraph (a)(i) to (iii) is no longer correct as a consequence of that establishment in the United Kingdom.

(2) Sub-paragraph (1) only applies if—

(a) the packaging and package leaflet met the requirements of Part 13 as to the matters specified in sub-paragraph (1)(a)(i) to (iii) immediately before exit day; and

(b) the holder of the traditional herbal registration, having established itself in the United Kingdom, does not otherwise need to make any changes to the outer or immediate packaging, or the package leaflet, as the case may be, during the transitional period.

(3) In this paragraph "the transitional period" means the period of 33 months beginning with exit day.

List of approved countries for traditional use of a herbal medicinal product on exit day

51.—(1) For the purpose of regulation 125A (list of approved countries for traditional use of a herbal medicinal product), the licensing authority must, for the transitional period, include each EEA State in the list it publishes under regulation 125A(1).

(2) The licensing authority must not, before the end of the transitional period, exercise its power under regulation 125A(3) to remove an EEA State from the list.

(3) In this paragraph, the transitional period is two years beginning with exit day.

Applications made for a traditional herbal registration before exit day to which Chapter 4 of Title III of the 2001 Directive applied

52.—(1) Sub-paragraph (2) applies where an application for a traditional herbal registration has been made before exit day and—

(a) regulation 130(12) and (13) (applications to be determined under Chapter 4 of Title III of the 2001 Directive) applied to that application before exit day; but

(b) a decision as specified in Article 28(5) of the 2001 Directive has not been adopted by the licensing authority before exit day.

(2) Where this sub-paragraph applies, the licensing authority must—

(a) where the procedure specified in Article 28(4) of the 2001 Directive has concluded before exit day in relation to that application, grant a traditional herbal registration in respect of that application as soon as reasonably practicable, and in any event before the end of the period of 30 days, beginning with exit day; or

(b) where the procedure specified in Article 28(4) of the 2001 Directive has not concluded before exit day, determine that application in accordance with Part 7 of these Regulations as soon as reasonably practicable, unless the applicant notifies the licensing authority in writing that they no longer want the application to proceed.

(3) In making a determination under sub-paragraph (2)(b), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the application as a consequence of its involvement in any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a reference member state or concerned member state in the making of that decision or agreement, under any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11 (advice and representations).

(4) In making a determination under sub-paragraph (2)(b), the licensing authority must take all reasonable steps to ensure that it makes a decision to grant or refuse a traditional herbal registration in the time period specified in regulation 130(1) as if it had applied to that application on the date on which the application was submitted.

Suspensions of traditional herbal registrations that have effect immediately before exit day that were imposed under Chapter 4 of Title III of the 2001 Directive

53. Where, immediately before exit day, a traditional herbal registration has been suspended pursuant to the procedures in Chapter IV of Title III of 2001 Directive, the suspension—

(a) continues to have effect on and after exit day in accordance with the terms on which it was imposed; and

(b) is to be treated as if it had been imposed by the licensing authority under Part 7 of these Regulations (traditional herbal registrations).

Referrals made under Article 31 of the 2001 Directive concerning the suspension, variation or revocation of a traditional herbal registration that have not concluded before exit day

54.—(1) Sub-paragraph (2) applies where—

(a) a specified matter has been referred under Article 31 of the 2001 Directive before exit day; but

(b) the procedure has not concluded before exit day.

(2) Where this sub-paragraph applies, the licensing authority must make a decision in respect of the specified matter in accordance with regulation 135 (revocation, variation and suspension of traditional herbal registration) as soon as reasonably practicable.

(3) In making a decision under regulation 135 in accordance with sub-paragraph (2), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the specified matter as a consequence of its involvement in any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a member state in the making of that decision or agreement, under any procedure provided for in Chapter 4 of Title III of the 2001 Directive;

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11 (advice and representations).

(4) Sub-paragraph (5) applies if the licensing authority is making a decision under regulation 135 of these Regulations in accordance with sub-paragraph (2) in a case where the Co-ordination Group for Mutual Recognition and Decentralised procedures has given an opinion in relation to the matter under Article 31 of the Directive.

(5) Where this sub-paragraph applies, the licensing authority may treat the opinion as if it were the opinion of the appropriate committee for the purposes of paragraph 5 of Schedule 11.

(6) Sub-paragraph (7) applies where—

(a) a specified matter has been referred under Article 31 of the 2001 Directive before exit day;

(b) the referral has concluded before exit day; but

(c) the licensing authority has not, before exit day, taken the steps necessary to give effect to that decision or that opinion (as the case may be).

(7) Where this sub-paragraph applies, the licensing authority must take the steps necessary as a result of the decision or opinion to suspend, revoke or vary the traditional herbal registration within the time period specified in Article 34(3) of the 2001 Directive where the decision or opinion requires steps to be taken in relation to a traditional herbal registration.

(8) In this paragraph—

"concluded before exit day", in relation to an Article 31 referral, means—

(a) a Commission decision as provided for in Article 34(3) of the 2001 Directive has been taken before exit day; or

(b) an opinion of the Co-ordination Group for Mutual Recognition and Decentralised Procedures, which constituted the end of the Article 31 referral procedure, has been given before exit day; and

"specified matter" means—

(a) a matter referred under Article 31 of the 2001 Directive before exit day that concerns a proposal to suspend, revoke or otherwise vary a traditional herbal registration; but

(b) does not include a referral made under Article 107i of the 2001 Directive.

Proposals to refer an application for a traditional herbal registration to the Committee for Herbal Medicinal Products and the procedure in Part 3 of Schedule 11 that were on-going at exit day

55.—(1) This paragraph applies where—

(a) the licensing authority has proposed to refer an application for a traditional herbal registration to the Committee on Herbal Medicinal Products in accordance with Article 16c(4) of the 2001 Directive before exit day; but

(b) that application has not been determined in accordance with Part 7 of these Regulations before exit day.

(2) Where the licensing authority has received an opinion of the Committee for Herbal Medicinal Products before exit day in relation to the application, it must take that decision in to account and determine that application.

(3) Where the licensing authority has not received an opinion of the Committee for Herbal Medicinal Products before exit day, notwithstanding the amendments made to Part 3 of Schedule 11 by the EU Exit Regulations, it may—

(a) proceed to determine the application, taking into account any proceedings that took place before exit day under Part 3 of Schedule 11 (prior to its amendment by the EU Exit Regulations), or any opinion of the Committee on Herbal Medicinal Products in relation to the application that is given on or after exit day; or

(b) it may refer the matter under regulation 130A in order to obtain the findings and advice of the appropriate committee before determining the application.

PART 10

Transitional provision in respect of pharmacovigilance

Interpretation of Part

56. In this Part, references to a "holder" are to the holder of a UK marketing authorisation or a traditional herbal registration.

Temporary exemption as to the location of an appropriately qualified person for pharmacovigilance

57.—(1) Sub-paragraph (2) applies to a holder of a UK marketing authorisation or traditional herbal registration—

(a) which was granted before exit day;

(b) that remains in force on exit day as a UK marketing authorisation or traditional herbal registration (as the case may be); and

(c) in respect of which, the holder had an appropriately qualified person for pharmacovigilance in respect of that authorisation or registration who, immediately before exit day, resided and operated in an EEA State.

(2) Where this sub-paragraph applies to a holder, that holder is to be treated as satisfying the requirements of regulation 182(2)(a), notwithstanding the amendments made to that provision by the EU Exit Regulations, for the transitional period, insofar as that holder would otherwise not meet those requirements solely because the appropriately qualified person responsible for pharmacovigilance in respect of that authorisation or registration resides and operates in an EEA State.

(3) In this regulation "the transitional period" means the period of 21 months beginning with exit day.

Referrals made under Article 107i of the 2001 Directive concerning the evaluation of data from pharmacovigilance activities which are not concluded before exit day

58.—(1) Sub-paragraph (2) applies where—

(a) a specified matter has been referred under Article 107i of the 2001 Directive (urgent Union procedure) before exit day; but

(b) that procedure has not concluded before exit day.

(2) Where this sub-paragraph applies, the licensing authority must make a decision in respect of the specified matter in accordance with regulation 68 or 135 (revocation, variation and suspension of UK marketing authorisation or traditional herbal registration) as soon as reasonably practicable.

(3) In making a decision under regulation 68 or 135 in accordance with sub-paragraph (2), the licensing authority must have regard to—

(a) any relevant information obtained by it before exit day in relation to the specified matter as a consequence of its involvement in any procedure provided for by, or referred to in, Section 4 of Chapter 3 of the 2001 Directive;

(b) any relevant decision made, or agreement reached, before exit day, where the United Kingdom participated as a member state in the making of that decision or agreement, under any procedure provided for by, or referred to in, Section 4 of Chapter 3 of the 2001 Directive; and

(c) any advice it receives from the appropriate committee pursuant to the procedures in Schedule 11 (advice and representations).

(4) Sub-paragraph (5) applies if the licensing authority is making a decision under regulation 68 or 135 in accordance with sub-paragraph (2) in a case where the Committee for Medicinal Products for Human Use or the Co-ordination Group for Mutual Recognition and Decentralised Procedures (as the case may be) has given a final opinion in relation to the matter.

(5) Where this sub-paragraph applies, the licensing authority may treat the opinion as if it were the opinion of the appropriate committee for the purposes of paragraph 5 of Schedule 11 (advice and representations).

(6) In making a determination under regulation 68 or 135 in accordance with sub-paragraph (2), the licensing authority may adopt or have regard to any decision made, or agreement reached, in relation to the specified matter under Section 4 of Chapter 3 of the 2001 Directive on or after exit day, notwithstanding that the United Kingdom did not participate in the making of that decision or agreement.

(7) Sub-paragraph (8) applies where—

(a) a specified matter has been referred under Article 107i of the 2001 Directive before exit day; and

(b) that referral has concluded before exit day; but

(c) the licensing authority has not, before exit day, taken the steps necessary to give effect to that decision or that opinion (as the case may be).

(8) Where this sub-paragraph applies, the licensing authority must take the steps necessary as a result of the decision or opinion to suspend, revoke or vary the UK marketing authorisation or traditional herbal registration—

(a) as soon as reasonably practicable, and, where relevant, within the time period specified in Article 34(3) of the 2001 Directive where a Commission decision requires steps to be taken in relation to a UK marketing authorisation that is not a converted EU marketing authorisation, or traditional herbal registration; or

(b) as soon as reasonably practicable, where a Commission decision or opinion requires steps to be taken in respect of a UK marketing authorisation that is a converted EU marketing authorisation.

(9) In this paragraph—

"concluded before exit day", in relation to an Article 107i referral, means—

(a) a Commission decision as provided for in Article 107k of the 2001 Directive has been taken before exit day; or

(b) an opinion of the Co-ordination Group for Mutual Recognition and Decentralised Procedures, which constituted the end of the Article 107i referral procedure in accordance with Article 107k(2), has been given before exit day;

"specified matter" means a referral made under Article 107i of the 2001 Directive on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities.

Matters on-going at exit day in respect of periodic safety update reports

59.—(1) Sub-paragraph (2) applies where—

(a) a holder has submitted a periodic safety update report under regulation 191 before exit day;

(b) that periodic safety report is, immediately before exit day, to be assessed in accordance with the single assessment procedure in Article 107e of the 2001 Directive;

(c) the procedure described in Article 107e(3) of the 2001 Directive has been completed before exit day; but

(d) the licensing authority has not yet taken the steps described in regulation 194 before exit day.

(2) Where this sub-paragraph applies, notwithstanding the revocation of regulation 194 (responding to a single assessment of PSUR under Article 107e of the 2001 Directive) by the EU Exit Regulations, the licensing authority must take the steps specified in regulation 194 in respect of the UK marketing authorisation or traditional herbal registration as soon as reasonably practicable.

(3) Sub-paragraph (4) applies where—

(a) a holder has submitted a periodic safety update report under regulation 191 before exit day;

(b) that periodic safety report is, immediately before exit day, to be assessed in accordance with the single assessment procedure in Article 107e of the 2001 Directive; and

(c) the procedure described in Article 107e(3) of the 2001 Directive has not been completed before exit day.

(4) Where this sub-paragraph applies, the licensing authority—

(a) may notify a holder falling within sub-paragraph (3)(a) of the need to provide to it such further information that the licensing authority specifies; and

(b) must, subject to sub-paragraph (5), assess the periodic safety update report in accordance with regulation 195 (obligations on licensing authority to assess PSURs) (as amended by the EU Exit Regulations) as soon as reasonably practicable.

(5) Information required under sub-paragraph (4)(a) must be provided before the end of whatever period the licensing authority may specify.

(6) In making a determination under regulation 195, where sub-paragraph (4) applies, the licensing authority may adopt or have regard to—

(a) any relevant information obtained by it before exit day in relation to the periodic safety report and the assessment of that report as a consequence of its involvement in any procedure provided for in Section 2 of Chapter III of the 2001 Directive;

(b) any relevant decision made, or agreement reached, in relation to the periodic safety update report or its assessment before exit day, where the United Kingdom participated as a member state in the making of that decision or agreement, under any procedure provided for in Section 2 of Chapter III of the 2001 Directive;

(c) any decision made, or agreement reached, in relation to that marketing authorisation or certificate of registration under Section 2 of Chapter III of the 2001 Directive on or after exit day, notwithstanding that the United Kingdom did not participate in the making of that decision or agreement.

Matters on-going at exit day in relation to draft study protocols under Article 107n and 107o of the 2001 Directive (submission of, and amendment to, draft study protocols for required studies)

60.—(1) Where the Pharmacovigilance Risk Assessment Committee has, before exit day—

(a) issued a letter endorsing a draft study protocol under Article 107n(2)(a) of the 2001 Directive;

(b) informed a holder that the study is a clinical trial under Article 107n(2)(c) of the 2001 Directive; or

(c) informed a holder of its endorsement of a substantial amendment to that protocol under Article 107o of the 2001 Directive,

the licensing authority is deemed to have accepted the draft study protocol, or the amended draft study protocol, or made that decision (as the case may be) under regulation 199(5) (submission of draft study protocols for required studies) or 200(5)(b) (amendment to study protocols for required studies).

(2) Where sub-paragraph (1) applies, the licensing authority may request the holder to provide to it any information in relation to the procedures under Article 107n or 107o of the 2001 Directive within a specified time period, and that holder must provide that information within that time period.

(3) Sub-paragraph (4) applies where, before exit day—

(a) a holder is proposing to, or, pursuant to Article 21a or 22a of the 2001 Directive, is under a duty to, undertake a non-interventional post-authorisation safety study; and

(b) the procedure specified in Article 107n or 107o of the 2001 Directive has not concluded before exit day.

(4) Where this sub-paragraph applies, on and after exit day, the holder must—

(a) submit any further information that has been required of it by the Pharmacovigilance Risk Assessment Committee to the licensing authority; and

(b) submit to the licensing authority such further information that it may request in relation to the procedures under Article 107n or 107o of the 2001 Directive within a time period specified by the licensing authority, whether or not that information has already been submitted to, or received from, that Committee before exit day,

and the licensing authority must assess that information in accordance with regulation 199 or 200 (as the case may be).

(5) In this paragraph, "not concluded before exit day" means that—

(a) a holder is proposing to, or, pursuant to Article 21a or 22a of the 2001 Directive, is under a duty to, undertake a non-interventional post-authorisation safety study;

(b) the Pharmacovigilance Risk Assessment Committee has not taken any of the steps specified in sub-paragraph (1)(a) to (c).

Matters on-going at exit day in respect of the follow up of final study reports

61.—(1) Sub-paragraph (2) applies where—

(a) a final study report has been submitted to the Pharmacovigilance Risk Assessment Committee under Article 107p of the 2001 Directive; but

(b) that committee has not, before exit day, made recommendations under Article 107q(1) of the 2001 Directive.

(2) Where this sub-paragraph applies—

(a) the licensing authority may, on or after exit day, request the holder to submit to it the information specified in regulation 201(2) (submission and evaluation of final study reports for required studies), and such further information relating to the final study report, or the procedure provided for in Chapter 4 of Title IX of the 2001 Directive, as the licensing authority may require; and

(b) that holder must, in any event, undertake the steps specified in regulation 201(5) in respect of that final study report.

(3) Sub-paragraph (4) applies where—

(a) regulation 202(1) (follow-up of final study reports) applied before exit day in respect of a final study report; but

(b) the licensing authority has not, before exit day, taken the steps specified in regulation 202(2).

(4) Where this paragraph applies, notwithstanding the revocation of regulation 202 by the EU Exit Regulations, the licensing authority must take the steps specified in regulation 202(2) in accordance with the time period specified in that paragraph.

(5) Sub-paragraph (6) applies where—

(a) regulation 202(3) applied before exit day; but

(b) the holder has not taken the steps specified in regulation 202(4) before exit day.

(6) Where this sub-paragraph applies, notwithstanding the revocation of regulation 202—

(a) the holder must take the steps specified in regulation 202(4); and

(b) the licensing authority must determine that application for a variation in accordance with Part 5 (marketing authorisations) or 7 (traditional herbal registrations).

PART 11

Transitional provision in respect of Part 12

Approved country health professional list on exit day (regulation 214(6A))

62.—(1) For the purposes of regulation 214(6A), for the transitional period, the licensing authority must include on the list published under that paragraph, professions of equivalent professional status to an appropriate practitioner under regulation 214(3) to (5D) in each EEA State.

(2) In this paragraph, "transitional period" is the period of one year beginning with exit day.

PART 12

General provision in relation to transitional provisions

Licensing authority power to require information

63.—(1) Notwithstanding any other power to require information under this Schedule, the licensing authority may require in writing that a holder of, or an applicant for, a UK marketing authorisation, parallel import licence, manufacturing licence, wholesale dealing licence, certificate of registration or traditional herbal registration provides it with any information which—

(a) is relevant to the exercise of the licensing authority's functions under this Schedule; and

(b) is either in the holder's or applicant's possession or is information which the holder or applicant may reasonably access,

within such time period as the licensing authority specifies in that written request.

(2) If the holder of an authorisation, licence, certificate or registration mentioned in sub-paragraph (1) fails to comply with a request made pursuant to that sub-paragraph, the licensing authority may suspend the authorisation, licence, certificate or registration until the holder complies with the obligation.

(3) Nothing in this Schedule requires a person to supply information in contravention of requirements imposed under the data protection legislation (within the meaning of Part 1 of the Data Protection Act 2018(**17**)).".

(**17**) 2018 c. 12.

SCHEDULE 8 Regulation 229

Consequential provision

PART 1

Amendment of primary legislation

Amendment of the National Health Service Act 2006

1.—(1) Section 88 of the National Health Service Act 2006(**18**) (GMS contracts: prescription of drugs, etc) is amended as follows.

(2) In subsection (3), for "Community marketing authorization or United Kingdom" substitute "UK".

(3) For subsection (4) substitute—

"(4) "UK marketing authorisation" has the meaning given by regulation 8(1) of the Human Medicines Regulations 2012 (S.I. 2012/1916)(**19**).".

Amendment of the Access to Medical Treatments (Innovation) Act 2016

2. In section 3(2)(b) and (4)(a), (b) and (c) of the Access to Medical Treatments (Innovation) Act 2016(**20**) (provision supplementary to section 2: database of innovative treatments) insert "UK" before "marketing authorisation".

PART 2

Amendment of secondary legislation

Amendment of the Medicines (Bal Jivan Chamcho Prohibition) (No 2) Order 1977

3. In article 2 of the Medicines (Bal Jivan Chamcho Prohibition) (No 2) Order 1977 (prohibition of sale, supply and importation of Bal Jivan Chamcho)(**21**)—

(a) for paragraph (4) substitute—

"(4) The prohibition imposed by paragraph (1) does not apply where the medicinal product—

(a) is imported from an approved country for import; and

(b) is being, or is to be, exported to a country other than the United Kingdom."; and

(b) for paragraph (5) substitute—

"(5) In paragraph (4), "approved country for import" has the meaning given in regulation 8(1) of the Human Medicines Regulations 2012.".

(**18**) 2006 c.41.
(**19**) S.I. 2012/1916.
(**20**) 2016 c.9.
(**21**) S.I. 1977/670. Article 2 was amended by S.I. 1990/2487, 1997/856, 2008/548 and 2012/1809.

Amendment of the Prescription Only Medicines (Human Use) Order 1997

4. In article 5(1) of the Prescription Only Medicines (Human Use) Order 1997 (exempt medicinal products)(**22**), insert "UK" before "marketing authorisation".

Amendment of the Medicines (Aristolochia and Mu Tong etc) (Prohibition) Order 2001

5.—(1) The Medicines (Aristolochia and Mu Tong etc) (Prohibition) Order 2001(**23**) is amended as follows.

(2) In article 1 (citation, commencement and interpretation)(**24**)—

(a) omit the definitions of "free circulation in member States" and "third country"; and

(b) insert at the appropriate place—

> ""approved country for import" has the meaning given in regulation 8(1) of the Human Medicines Regulations 2012;".

(3) In article 4 (exceptions to the prohibition imposed by articles 2 and 3)(**25**)—

(a) for paragraph (3) substitute—

> "(3) The prohibition imposed by articles 2 and 3 does not apply where the medicinal product—
>
> (a) is imported from an approved country for import; and
>
> (b) is being, or is to be, exported to a country other than the United Kingdom."; and

(b) in paragraph (4), for "marketing authorisation, certificate of registration, traditional herbal registration or Article 126a authorisation" substitute "UK marketing authorisation, certificate of registration or traditional herbal registration".

Amendment of the Medicines for Human Use (Kava-kava) (Prohibition) Order 2002

6.—(1) The Medicines for Human Use (Kava-kava) Prohibition) Order 2002(**26**) is amended as follows.

(2) In article 1 (citation, commencement and interpretation)(**27**)—

(a) omit the definitions of "free circulation in member States" and "third country"; and

(b) insert at the appropriate place—

> ""approved country for import" has the meaning given in regulation 8(1) of the Human Medicines Regulations 2012;".

(3) In article 3 (exceptions to the prohibition imposed by article 2)(**28**)—

(a) for paragraph (c) substitute—

> "(c) imported from an approved country for import, and is being, or is to be, exported to a country other than the United Kingdom; or"; and

(b) in paragraph (d), for "marketing authorisation, certificate of registration, traditional herbal registration or Article 126a authorisation" substitute "UK marketing authorisation, certificate of registration or traditional herbal registration".

(**22**) S.I. 1997/1830. Article 5(1) was amended by S.I. 2012/1916.
(**23**) S.I. 2001/1841.
(**24**) Article 1 was amended by S.I. 2008/548 and 2012/1809.
(**25**) Article 4 was amended by S.I. 2008/548 and 2012/1916.
(**26**) S.I. 2002/3170.
(**27**) Article 1 was amended by S.I. 2008/548 and 2012/1809.
(**28**) Article 3 was amended by S.I. 2008/548 and 2012/1916.

Amendment of the Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003

7. In regulation 1(2) of the Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 (citation, commencement and interpretation)(**29**), in the definition of "unlicensed product"—

(a) in paragraph (a) for "marketing authorization" substitute "UK marketing authorisation"; and

(b) omit paragraphs (a)(ii) and (d).

Amendment of the Blood Safety and Quality Regulations 2005

8. In regulation 1A of the Blood Safety and Quality Regulations 2005(**30**), after paragraph (10) insert—

"(10A) Paragraph 7.1 is to be read as if reference to "Directive 2003/94/EC" were to "the Good Manufacturing Practice Directive, within the meaning of regulation 8(1) of the Human Medicines Regulations 2012.".

Amendment of the Natural Mineral Water, Spring Water and Bottled Drinking Water (England) Regulations 2007

9. In regulation 3(1)(a) of the Natural Mineral Water, Spring Water and Bottled Drinking Water (England) Regulations 2007 (exemptions)(**31**) for "Directive" to the end substitute "regulation 2(1) of the Human Medicines Regulations 2012".

Amendment of the Medicines for Human Use (Prohibition) (Senecio and Miscellaneous Amendments) Order 2008

10.—(1) The Medicines for Human Use (Prohibition) (Senecio and Miscellaneous Amendments) Order 2008(**32**) is amended as follows.

(2) In article 1 (citation, commencement and interpretation)(**33**)—

(a) omit the definitions of "free circulation in member States" and "third country"; and

(b) insert at the appropriate place—

""approved country for import" has the meaning given in regulation 8(1) of the Human Medicines Regulations 2012;".

(3) In article 3 (exceptions to the prohibition imposed by article 2)(**34**)—

(a) for paragraph (c) substitute—

"(c) is imported from an approved country for import, and is being, or is to be, exported to a country other than the United Kingdom; or"; and

(b) in paragraph (d), for "marketing authorisation, certificate of registration, traditional herbal registration or Article 126a authorisation" substitute "UK marketing authorisation, certificate of registration or traditional herbal registration".

(**29**) S.I. 2003/1680. Regulation 2(1) has been previously amended by S.I. 2004/3224, 2005/2750 and 2754 and 2012/1916.
(**30**) S.I. 2005/50. Regulation 1A was inserted by S.I. 2019/4.
(**31**) S.I. 2007/2785. Regulation 3(1)(a) was substituted by S.I. 2018/352.
(**32**) S.I. 2008/548.
(**33**) Article 1 was amended by S.I. 2012/1809.
(**34**) Article 3 was amended by S.I. 2012/1916.

Amendment of the National Health Service (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013

11.—(1) The National Health Service (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013(**35**) are amended as follows.

(2) In paragraph 8(10) of Schedule 4 (terms of service of NHS pharmacists: providing ordered drugs or appliances), insert "UK" before "marketing authorisation" in both places it appears.

(3) In paragraph 6(8) of Schedule 7 (mandatory terms for LPS schemes: providing ordered drugs or appliances), insert "UK" before "marketing authorisation" in both places it appears.

Amendment of the Genetically Modified Organisms (Contained Use) Regulations 2014

12. In regulation 3(2)(b) of the Genetically Modified Organisms (Contained Use) Regulations 2014 (application)(**36**), at the end insert—

"; or

(iv) a medicinal product for human use marketed in accordance with the Human Medicines Regulations 2012;".

Amendment of the Nicotine Inhaling Products (Age of Sale and Proxy Purchasing) Regulations 2015

13.—(1) The Nicotine Inhaling Products (Age of Sale and Proxy Purchasing) Regulations 2015(**37**) are amended as follows.

(2) In regulation 1(4) (citation, commencement and interpretation), insert "UK" before "marketing authorisation".

(3) In regulation 5(2)(c)(i) (exception for medicines indicated for the treatment of persons under 18), insert "UK" before "marketing authorisation".

Amendment of the Genetically Modified Organisms (Contained Use) Regulations (Northern Ireland) 2015

14. In regulation 3(2)(b) of the Genetically Modified Organisms (Contained Use) Regulations (Northern Ireland) 2015 (application)(**38**), at the end insert—

"; or

(iv) a medicinal product for human use marketed in accordance with the Human Medicines Regulations 2012;".

Amendment of the Health Service Products (Provision and Disclosure of Information) Regulations 2018

15. In regulation 29(4) of the Health Service Products (Provision and Disclosure of Information) Regulations 2018(**39**)—

(a) in the definition of "notifiable presentation"—

(i) insert "UK" before "marketing authorisation", and

(ii) omit from "other than" to the end;

(**35**) S.I. 2013/349.
(**36**) S.I. 2014/1663.
(**37**) S.I. 2015/895.
(**38**) S.R. 2015 No. 339.
(**39**) S.I. 2018/677.

(b) in the definition of "designated producer" insert "UK" before "marketing authorisation"; and

(c) in the definition of "marketing authorisation" insert "UK" before "marketing".

Amendment of the Branded Health Service Medicines (Costs) Regulations 2018

16.—(1) The Branded Health Service Medicines (Costs) Regulations 2018(**40**) are amended as follows.

(2) In regulation 1(2) (interpretation)—

(a) in the definition of "marketing authorisation" insert "UK" before "marketing" and re-insert the definition at the appropriate place;

(b) in the definition of "marketing authorisation holder" insert "UK" before "marketing" in and re-insert the definition at the appropriate place;

(c) omit the definition of "parallel distributed presentation";

(d) in paragraph (b) of the definition of "relevant medicine" insert "UK" before "marketing authorisation"; and

(e) in the definition of "supplementary protection certificate" omit from "means" to the end and insert "has the meaning given by section 128B(2) of the Patents Act 1977".

(3) In regulation 3 (payment scheme)—

(a) in paragraph (3)(a), insert "UK" before "marketing authorisation holder";

(b) omit paragraph (4)(c).

(4) In regulation 9 (new presentation)—

(a) in paragraph (10)—

(i) in sub-paragraph (a), insert at the beginning "in relation to a product in respect of which there is a converted EU marketing authorisation",

(ii) in sub-paragraph (b), for "Article 21" to the end substitute "regulation 64(6) of the 2012 Regulations"; and

(b) in paragraph (12), insert before the definition of "licensing authority"—

""converted EU marketing authorisation" has the meaning given in paragraph 6(1) and (2) of Schedule 33A to the 2012 Regulations;".

(5) In regulation 21 (sales report), omit paragraph (1)(h).

(6) In regulation 22 (presentation report), omit sub-paragraph (h).

SCHEDULE 9 Regulation 230

Retained EU law: revocations

1. Insofar as they apply to medicinal products for human use, and subject to the transitional provisions in Schedule 33A to the Human Medicines Regulations 2012(**41**), the following instruments are revoked—

(a) Council Decision 75/320/EEC of 20 May 1975 setting up a Pharmaceutical Committee;

(**40**) S.I. 2018/345.
(**41**) S.I. 2012/1916.

(b) Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the evaluation of medicinal products;

(c) Commission Regulation (EC) No 1662/95 of 7 July 1995 laying down certain detailed arrangements for implementing the Community decision-making procedures in respect of marketing authorisations for products for human or veterinary use;

(d) Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorisation for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93;

(e) Council Regulation (EC) No 2743/98 of 14 December 1998 amending Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products;

(f) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products;

(g) Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority';

(h) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency;

(i) Council Regulation (EC) No 1905/2005 of 14 November 2005 amending Regulation (EC) No 297/95 on fees payable to the European Medicines Agency;

(j) Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises;

(k) Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council;

(l) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004;

(m) Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation (EC) No 1901/2006 on medicinal products for paediatric use;

(n) Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council;

(o) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) NO 726/2004;

(p) Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicines;

(q) Commission Regulation (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the

evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises;

(r) Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency and Regulation (EC) No 1394/2007 on advanced therapy medicinal products;

(s) Commission Regulation (EU) No 488/2012 of 8 June 2012, amending Regulation (EC) no 658/2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council;

(t) Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council;

(u) Commission Regulation (EU) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products;

(v) Regulation (EU) N0 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance;

(w) Commission Implementing Decision of 22 November 2012 establishing a list of third countries with a regulatory framework applicable to active substances for medicinal products for human use and the respective control and enforcement activities ensuring a level of protection of public health equivalent to that in the Union, in accordance with Directive 2001/83/EC;

(x) Commission Implementing Decision of 23 January 2013 on the assessment of a third country's regulatory framework applicable to active substances of medicinal products for human use and of the respective control and enforcement activities pursuant to Article 111b of Directive 2001/83/EC;

(y) Commission Implementing Regulation (EU) No 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicinal products for human use that are subject to additional monitoring;

(z) Commission implementing Decision of 24 April 2013 amending implementing Decision 2012/715/EU establishing a list of third countries with a regulatory framework applicable to active substances for medicinal products for human use and the respective control and enforcement activities ensuring a level of protection of public health equivalent to that in the Union;

(aa) Commission implementing Decision of 4 June 2013 amending implementing Decision 2012/715/EU establishing a list of third countries with a regulatory framework applicable to active substances for medicinal products for human use and the respective control and enforcement activities ensuring a level of protection of public health equivalent to that in the Union;

(bb) Commission implementing Decision of 11 June 2013 amending implementing Decision 2012/715/EU establishing a list of third countries with a regulatory framework applicable to active substances for medicinal products for human use and the respective control and enforcement activities ensuring a level of protection of public health equivalent to that in the Union;

(cc) Commission Delegated Regulation (EC) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required;

(dd) Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use(**42**);

(ee) Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83 with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use;

(ff) Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014 on the design of the common logo to identify persons offering medicinal products for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity;

(gg) Commission implementing Decision of 1 July 2015 amending implementing Decision 2012/715/EU establishing a list of third countries with a regulatory framework applicable to active substances for medicinal products for human use and the respective control and enforcement activities ensuring a level of protection of public health equivalent to that in the Union;

(hh) Commission Delegated Regulation (EU) No 2016/161 of 2 October 2015 supplementing Directive 2001/83 of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use;

(ii) Commission Regulation (EU) 2018/781 of 29 May 2018 amending Regulation (EC) No 847/2000 as regards the definition of the concept "similar medicinal product".

(**42**) OJ No, L 189, 27.6.2014, p. 112.