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.".