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COMMISSION DELEGATED REGULATION (EU) 2024/1701

of 11 March 2024

amending Regulation (EC) No 1234/2008 as regards the examination of variations to the terms of marketing authorisations for medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use ([1]), and in particular Article 23b(2a) thereof,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency ([2]), and in particular Article 16a(3) thereof,

Whereas:

(1) The Union legal framework regarding variations to the terms of marketing authorisations is laid down in Commission Regulation (EC) No 1234/2008 ([3]). In the light of practical experience in the application of that Regulation, it is appropriate to proceed to its review in order to establish a simpler, clearer and more flexible legal framework, while guaranteeing the same level of public health protection.

(2) The procedures laid down in Regulation (EC) No 1234/2008 should therefore be adjusted, without departing from the general principles on which those procedures are based.

(3) In order to achieve efficiency gains and to reduce the administrative burden for the pharmaceutical industry and to better use the resources of the competent authorities, the existing legal framework should be simplified and streamlined, ensuring the same standards for quality, efficacy and safety of medicines.

(4) In order to constantly take account of scientific and technical progress and to ensure the streamlined procedures of variations, the classification guidelines may need to be updated more frequently on the basis of this knowledge. For this purpose, the Agency should provide annual recommendations on unforeseen variations and any updates to be integrated in the guidelines and published in the electronic version on the Commission website.

(5) Grouping of several variations in a single submission is already possible in certain cases. However, practical experience and knowledge acquired from the worksharing procedure have shown that the grouping of variations could be extended to enable more flexibility and to increase harmonisation. Therefore, the submission of a single submission of variations to the terms of more than one marketing authorisation ('super-grouping of variations') should be introduced in order to enable marketing authorisation holders to include their purely national marketing authorisation in the super-grouping of variations and to harmonise their purely national marketing authorisations in different Member States.

([1]) OJ L 311, 28.11.2001, p. 67, ELI: http://data.europa.eu/eli/dir/2001/83/oj.
([2]) OJ L 136, 30.4.2004, p. 1, ELI: http://data.europa.eu/eli/reg/2004/726/oj.
([3]) 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 medicinal products (OJ L 334, 12.12.2008, p. 7, ELI: http://data.europa.eu/eli/reg/2008/1234/oj).

(6) The variations worksharing procedure enables already today the single submission of variations to the terms of more than one marketing authorisation owned by the same marketing authorisation holder. In order to avoid duplication of work in the evaluation of variations, it should be possible for competent authorities to process all appropriate variations under the worksharing procedure.

(7) Advances in science and technology and decades of experience in the manufacture of biological medicinal products enables the application of a risk-based approach for quality changes related to those biological medicinal products. Therefore, it is appropriate to adapt the approach of classifying some of the quality changes related to biological medicinal products as, by default, major variations. This will apply to all biological medicines including advanced therapy medicines.

(8) Based on the experience gained from the COVID-19 pandemic and the adaptations to the variation systems that have been made to ensure the continued effectiveness of vaccines by changing their composition so as to protect against new or multiple variant strains in the context of that pandemic or otherwise, similar possibilities to change the composition should be introduced for other vaccines to address a public health emergency.

(9) In line with the approach taken with human influenza vaccines, updates of human coronavirus vaccines should be streamlined outside a public health emergency. Thus, also the examination of variations concerning changes to the active substance for the purposes of the annual update of a human coronavirus vaccine should follow the same rules as influenza vaccines when the Agency considers it necessary from the public health perspective and takes into account global approaches to updates of human coronavirus vaccines.

(10) It is necessary to take account of developments arising as a result of efforts to align at international level the life-cycle management of medicinal products, especially in the context of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This may be supported by the use of additional regulatory tools, such as post-approval change management protocols.

(11) Regulation (EU) 2019/5 of the European Parliament and of the Council ([4]) moved certain core elements of the system for examination of applications for variations provided for in Regulation (EC) No 1234/2008 into Directive 2001/83/EC and Regulation (EC) No 726/2004. A delegation of powers is conferred on the Commission in Directive 2001/83/EC and Regulation (EC) No 726/2004 to complement those core elements by laying down further necessary elements and to adapt the system for examination of applications for variations to technical and scientific progress. In order to avoid any duplication, it is appropriate to delete those elements from Regulation (EC) No 1234/2008. In view of the changes introduced by Regulation (EU) 2019/6 of the European Parliament and of the Council ([5]), which provides that Regulation (EC) No 1234/2008 is to no longer apply to veterinary medicinal products, any references to veterinary medicinal products should be removed from Regulation (EC) No 1234/2008.

(12) A transitional period should be established in order to give all interested parties, in particular competent authorities of the Member States and the pharmaceutical industry, time to adapt to the new legal framework.

(13) Regulation (EC) No 1234/2008 should therefore be amended accordingly,

([4]) Regulation (EU) 2019/5 of the European Parliament and of the Council of 11 December 2018 amending 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, Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Directive 2001/83/EC on the Community code relating to medicinal products for human use (OJ L 4, 7.1.2019, p. 24, ELI: http://data.europa.eu/eli/reg/2019/5/oj).

([5]) Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 4, 7.1.2019, p. 43, ELI: http://data.europa.eu/eli/reg/2019/6/oj).

HAS ADOPTED THIS REGULATION:

Article 1

Regulation (EC) No 1234/2008 is amended as follows:

(1) the title is replaced by the following:

'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';

(2) Article 1 is amended as follows:

(a) paragraph 1 is replaced by the following:

'1. This Regulation lays down provisions concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use granted in accordance with Regulation (EC) No 726/2004 or Directive 2001/83/EC.';

(b) paragraph 3 is replaced by the following:

'3. Chapter II shall apply only to variations to the terms of marketing authorisations granted in accordance with Chapter 4 of Directive 2001/83/EC.';

(3) Article 2 is amended as follows:

(a) the introductory wording is replaced by the following:

'For the purposes of this Regulation, the definitions in Article 1 of Directive 2001/83/EC shall apply.

The following definitions shall also apply:';

(b) paragraph 1 is deleted;

(c) the following paragraph (6a) is inserted:

'6a. "Reference authority" means:

(a) the Agency where at least one of the marketing authorisations concerned is a centralised marketing authorisation;

(b) the competent authority of the Member State chosen by the holder and accepted by that competent authority, or chosen by the coordination group referred to in Article 27 of Directive 2001/83/EC if none of the competent authorities of the Member States agrees to act as the reference authority, in the other cases;';

(4) in Article 3(3), point (b) is replaced by the following:

'(b) where the competent authority of the reference Member State referred to in Article 28 of Directive 2001/83/EC ("the reference Member State"), in consultation with the other Member States concerned, or the Agency in the case of a centralised marketing authorisation, or the competent authority in the case of a purely national marketing authorisation, concludes, following the assessment of validity of a notification in accordance with Article 9(1), Article 13b(1), or Article 15(1) of this Regulation and taking into account the recommendations delivered pursuant to Article 5, that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.';

(5) Article 4 is amended as follows:

(a) in paragraph 2, the following second and third subparagraphs are added:

'The Agency, in cooperation with the competent authorities of the Member States, shall report annually to the Commission on recommendations on unforeseen variations referred to in Article 5 that result in new classification of variations and provide information on necessary updates to be included in the guidelines referred to in paragraph 1.

The Commission shall without undue delay consider the report and integrate new classification of variations and necessary updates to the guidelines.';

(b) the following paragraph 3 is added:

'3. The Commission may publish the electronic version of the guidelines on its website. This electronic version may include new classification of variations and necessary updates to the guidelines before the regular update pursuant to paragraph 2.';

(6) Article 5 is amended as follows:

(a) paragraph 1 is replaced by the following:

'1. Prior to the submission of a variation whose classification is not provided for in this Regulation, a holder may request a recommendation on the classification of the variation as follows:

(a) from the Agency, where the variation refers to a marketing authorisation granted under Regulation (EC) No 726/2004;

(b) from the competent authority of the Member State concerned, where the variation refers to a purely national marketing authorisation;

(c) from the competent authority of the reference Member State, in the other cases.

Where a recommendation is requested from the Agency as set out in the first subparagraph, point (a), it shall consult the coordination group if the recommendation is expected to result in a new classification of variation.

Where a recommendation is requested from the competent authority of the Member State concerned or of the reference Member State as set out in the first subparagraph, points (b) and (c), the relevant authority shall consult the coordination group and the Agency, if the recommendation is expected to result in a new classification of variation.

The recommendations shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within 60 days following receipt of the request and sent to the holder, the Agency, and the coordination group.';

(b) in paragraph 1a, the second subparagraph is replaced by the following:

'The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within 60 days following receipt of the request and sent to the holder, the Agency, and the competent authorities of all Member States.';

(c) the following paragraph 3 is added:

'3. The recommendation referred to in paragraph 1 that results in a new classification of variation shall be regularly integrated in the guidelines referred to in Article 4(1) in accordance with Article 4(2), third subparagraph.';

(7) the following Article 6a is inserted:

'*Article 6a*

Additional regulatory tools

For certain changes to the chemical, pharmaceutical and biological information for a medicinal product a holder may rely on a range of process parameters, quality attributes, protocols or summary documents, upon agreement of the relevant authority and subject to the conditions referred to in the Annexes and the guidelines referred to in Article 4(1) with regard to the specific regulatory tool.';

(8) in Article 7(2), point (a) is replaced by the following:

'(a) where minor variations of type IA to the terms of the same marketing authorisation are notified at the same time, a single notification as referred to in Article 8 or 14 may cover all such variations;';

(9) the following Article 7a is inserted:

'*Article 7a*

Super-grouping of variations

1. By way of derogation from Articles 7 and 13d, the holder may submit a single notification of variations to the terms of more than one marketing authorisation referred to in Chapters II, IIa and III owned by the same holder where the same or several minor variations of type IA referred to in Article 8, Article 13a or Article 14 are notified at the same time and fall within one of the cases of super-grouping of variations listed in the guidelines referred to in Article 4(1) ("super-grouping").

2. A single notification as referred to in paragraph 1 shall be made simultaneously to the reference authority and all relevant authorities.';

(10) the title of Chapter II is replaced by the following:

'CHAPTER II

VARIATIONS TO MARKETING AUTHORISATIONS GRANTED IN ACCORDANCE WITH CHAPTER 4 OF DIRECTIVE 2001/83/EC';

(11) in Article 8, paragraph 1 is replaced by the following:

'1. Where a minor variation of type IA is made, the holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV. That notification shall be submitted within 12 months following the implementation of the variation as an annual update for all minor variations of type IA or be submitted as part of grouping of variations in accordance with Article 7(2), first subparagraph, points (b) and (c), or as part of super-grouping of variations in accordance with Article 7a.

The notification shall 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.

By way of derogation from the first subparagraph, in justified cases, the competent authority of the reference Member State may accept the immediate submission of the notification after the implementation of the variation.';

(12) in Article 10(2) is amended as follows:

(a) the second subparagraph is replaced by the following:

'The competent authority of the reference Member State may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or may extend it to 90 days for variations listed in Annex V or for grouping of variations in accordance with Article 7(2), first subparagraph, point (c).';

(b) the third subparagraph is deleted;

(13) in Article 13, paragraphs 1 and 2 are replaced by the following:

'1. Where recognition of a decision in accordance with Article 10(4) or approval of an opinion in accordance with Article 20(8), point (b), is not possible on grounds of a potential serious risk to public health, a relevant authority shall request that the matter of disagreement be forthwith referred to the coordination group.

The party in disagreement shall give a detailed statement of the reasons for its position to all Member States concerned and to the holder.

2. Article 29(3), (4) and (5) of Directive 2001/83/EC shall apply to the matter of disagreement referred to in paragraph 1.';

(14) in Article 13a, paragraph 1 is replaced by the following:

'1. Where a minor variation of type IA is made, the holder shall submit to the competent authority a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following the implementation of the variation as an annual update for all minor variations of type IA or be submitted as part of grouping in accordance with Article 13d(2), first subparagraph, points (b) and (c), or as part of super-grouping of variations in accordance with Article 7a.

The notification shall 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.

By way of derogation from the first subparagraph, in justified cases, the competent authority of the Member State may accept the immediate submission of the notification after the implementation of the variation.';

(15) in Article 13c, paragraph 2 is amended as follows:

(a) the second subparagraph is replaced by the following:

'The competent authority may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or may extend it to 90 days for variations listed in Annex V or for grouping of variations in accordance with Article 13d(2), first subparagraph, point (c).';

(b) the third subparagraph is deleted;

(16) in Article 14, paragraph 1 is replaced by the following:

'1. Where a minor variation of type IA is made, the holder shall submit to the Agency a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following implementation of the variation as an annual update for all minor variations of type IA or be submitted as part of grouping in accordance with Article 7(2), first subparagraph, points (b) and (c), or as part of super-grouping of variations in accordance with Article 7a.

The notification shall 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.

By way of derogation from the first subparagraph, in justified cases, the Agency may accept the immediate submission of the notification of the variation.';

(17) Article 16 is amended as follows:

(a) paragraph 2 is amended as follows:

(a) the second subparagraph is replaced by the following:

'The Agency may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or may extend it to 90 days for variations listed in Annex V or for grouping of variations in accordance with Article 7(2), first subparagraph, point (c).';

(b) the third subparagraph is deleted;

(b) in paragraph 4, the first subparagraph is replaced by the following:

'Article 9(1) and (2) of Regulation (EC) No 726/2004 shall apply to the opinion on the valid application.';

(18) Article 17 is amended as follows:

(a) in paragraph 1, point (c) is replaced by the following:

'(c) where the outcome of the assessment is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency shall transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents set out in Article 9(4) of Regulation (EC) No 726/2004.';

(b) paragraph 2 is replaced by the following:

'2. In the cases identified under paragraph 1, point (c), the Commission, having regard to the opinion from the Agency and within the time limit provided for in Article 23(1a), shall amend where necessary the decision granting the marketing authorisation. The Union Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 shall be updated accordingly.';

(19) Article 18 is amended as follows:

(a) the title is replaced by the following:

'**Human influenza and human coronavirus vaccines**';

(b) paragraph 1 is replaced by the following:

'1. By way of derogation from Article 16, the procedure laid down in paragraphs 2 to 6 of this Article shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza or human coronavirus vaccine.

For annual updates of human coronavirus vaccines that procedure shall only apply after a public announcement of the Agency. The announcement shall be published on the Agency's webportal and include the timeframe for application.';

(c) paragraph 4 is replaced by the following:

'4. Within 55 days from the receipt of a valid application, the Agency shall adopt an opinion. The Agency's opinion on the application shall be transmitted to the holder. Where the Agency's opinion is favourable, the Agency shall also transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents set out in Article 9(4) of Regulation (EC) No 726/2004.';

(d) paragraph 6 is replaced by the following:

'6. Having regard to the favourable opinion of the Agency, the Commission shall amend where necessary the decision granting the marketing authorisation. The Union Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 shall be updated accordingly.';

(20) Article 20 is amended as follows:

(a) in paragraph 1, the introductory wording is replaced by the following:

'By way of derogation from Articles 7(1) and Articles 9, 10, 13b, 13c, 13d, 15 and 16 the holder shall follow the worksharing procedure laid down in paragraphs 3 to 9 of this Article in the following cases:';

(b) paragraph 2 is deleted;

(c) paragraphs 4 and 5 are replaced by the following:

'4. The reference authority shall issue an opinion on a valid application as referred to in paragraph 3 within a period that corresponds to the assessment period of the highest type of variation included following acknowledgement of receipt of a valid application in the case of minor variations of type IB or major variations of type II.

5. The reference authority may reduce the period referred to in paragraph 4, having regard to the urgency of the matter, or may extend it to 90 days for variations listed in Annex V or for grouping of variations in accordance with Article 7(2), first subparagraph, point (c), or Article 13d(2), first subparagraph, point (c).';

(d) in paragraph 6, point (c) is replaced by the following:

'(c) the reference authority may extend the period referred to in paragraph 4 to 90 days.';

(e) paragraph 7 is replaced by the following:

'7. Where the reference authority is the Agency, Article 9(1) and (2) of Regulation (EC) No 726/2004 shall apply to the opinion referred to in paragraph 4.

The Agency's opinion on the application shall be transmitted to the holder and the Member States, together with the assessment report. Where the outcome of the assessment is favourable and the variation affects the terms of a Commission decision granting the marketing authorisation, the Agency shall also transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents set out in Article 9(4) of Regulation (EC) No 726/2004.

Where the Agency issues a favourable opinion, the following shall apply:

(a) if the opinion recommends the variation to the terms of a Commission decision granting the marketing authorisation, the Commission shall, having regard to the final opinion and within the time limits provided for in Article 23(1a), amend the decision accordingly, provided that the revised versions of the documents set out in Article 9(4) of Regulation (EC) No 726/2004 have been received. The Union Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 shall be updated accordingly;

(b) the Member States concerned shall, within 60 days following receipt of the final opinion of the Agency, approve that final opinion, inform the Agency thereof and, where necessary, amend the marketing authorisations concerned accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned.';

(f) the following paragraph 11 is added:

'11. In justified cases, in accordance with the guidelines referred to in Article 4(1), when agreed by the competent authorities of the Member States and the Agency, the holder may choose to follow the worksharing procedure laid down in paragraphs 3 to 9 for the marketing authorisations referred to in Chapters II, IIa and III, where a minor variation of type IB, a major variation of type II, or a group of variations where at least one of the variations is a minor variation of type IB or a major variation of type II that does not contain any extension, relates to several marketing authorisations owned by several holders in more than one Member State.';

(21) Article 21 is replaced by the following:

'*Article 21*

Public health emergency

1. By way of derogation from Chapters I, II, IIa and III, where a public health emergency at Union level is recognised by the Commission pursuant to Regulation (EU) 2022/2371 of the European Parliament and of the Council (*) the relevant authorities, or in the case of centralised marketing authorisations, the Commission may, where certain pharmaceutical, non-clinical or clinical data are missing, exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human vaccine pertaining to the pathogen causing the public health emergency.

2. The relevant authority may request the holder to provide supplementary information in order to complete its assessment within a time limit set by it.

3. Variations may be accepted pursuant to paragraph 1 only if the benefit-risk balance of the medicinal product is favourable.

4. Where a variation is accepted pursuant to paragraph 1, the holder shall submit the missing pharmaceutical, non-clinical and clinical data within a time limit set by the relevant authority.

5. In the case of centralised marketing authorisations, the missing data and the time limit for submission or compliance shall be specified in the conditions to the marketing authorisation. Where the marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No 726/2004 this may be done as part of the specific obligations referred to in paragraph 4 of that Article.

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(*) Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26, ELI: http://data.europa.eu/eli/reg/2022/2371/oj).';

(22) Article 22 is amended as follows:

(a) in paragraph 1, the first subparagraph is replaced by the following:

'Where, in the event of a risk to public health in the case of medicinal products, the holder takes urgent safety restrictions on its own initiative, it shall forthwith inform all relevant authorities and, in the case of a centralised marketing authorisation, the Agency.';

(b) paragraph 2 is replaced by the following:

'2. In the event of a risk to public health in the case of medicinal products, relevant authorities or, in the case of centralised marketing authorisations, the Commission may impose urgent safety restrictions on the holder.';

(23) in Article 23(1a), point (a) is amended as follows:

(a) points (iv), (v) and (vii) are deleted;

(b) point (viii) is replaced by the following:

'(viii) other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern;';

(c) the following point (x) is added:

'(x) variations related to the replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences of a human vaccine that has the potential to address a public health emergency;';

(24) in Article 23a, the following title is inserted:

'**Compliance with the paediatric investigation plan**';

(25) in Article 24(5), the second subparagraph is replaced by the following:

'By way of derogation from the first subparagraph, urgent safety restrictions and variations related to safety issues which concern marketing authorisations granted in accordance with Chapter 4 of Directive 2001/83/EC shall be implemented within a time frame agreed by the holder and the competent authority of the reference Member State, in consultation with the other relevant authorities.';

(26) Article 26 is deleted;

(27) Annexes I, II, and III are amended in accordance with Annex I to this Regulation;

(28) Annex V is replaced by the text set out in Annex II to this Regulation.

Article 2

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 1 January 2025.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 11 March 2024.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX I

Annexes I, II, and III to Regulation (EC) No 1234/2008 are amended as follows:

(1) Annex I is amended as follows:

(a) in point 1, point (c) is replaced by the following:

'(c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy or safety characteristics are not significantly different, with the exception of the following:

— changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

— replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine;

— replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences, for a human vaccine other than for human influenza or coronavirus that has the potential to address a public health emergency in the Union;';

(b) in point 2, point (e) is replaced by the following:

'(e) change or addition of a new route of administration (*).

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(*) For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes.';

(c) point 3 is deleted;

(2) Annex II is amended as follows:

(a) point 1 is amended as follows:

(i) point (f) is replaced by the following:

'(f) 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;';

(ii) the following point (g) is added:

'(g) variations related to changes to a medical device that is an integral part of or in exclusive use with the medicinal product which have no impact on the quality, safety or efficacy of the medicinal product.';

(b) point 2 is amended as follows:

(i) point (e) is deleted;

(ii) point (f) is replaced by the following:

'(f) variations related to the introduction of a new design space, where the design space has been developed in accordance with the relevant European and international scientific guidelines;';

(iii) the following point (fa) is inserted after point (f):

'(fa) variations related to the introduction of a post approval change management protocol where the protocol has been developed in accordance with the relevant European and international scientific guidelines;';

(iv) points (g), (h), (i) and (k) are deleted;

(v) point (l) is replaced by the following:

'(l) variations related to the replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine;';

(vi) the following points (m) and (n) are added:

'(m) variations related to the replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences of a human vaccine that has the potential to address a public health emergency;

(n) variations related to changes to a medical device that is an integral part of or in exclusive use with the medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product.';

(3) Annex III is amended as follows:

(a) points 6, 7 and 8 are replaced by the following:

'6. All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substances, including related administrative changes.

7. All variations in the group are changes affecting the quality of a human pandemic influenza or coronavirus vaccine.

8. All variations in the group are changes to the pharmacovigilance system referred to in Article 8(3), point (ia) of Directive 2001/83/EC.';

(b) point 13 is deleted;

(c) point 14 is replaced by the following:

'14. All variations in the group are consequential to a specific procedure or condition carried out pursuant to Article 14(8) of Regulation (EC) No 726/2004 or Article 22 of Directive 2001/83/EC.'.

ANNEX II

'ANNEX V

Variations concerning a change to or addition of therapeutic indications.'.