

REGULATION ON VARIATIONS TO LICENSED HUMAN MEDICINAL PRODUCTS

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SECTION ONE Objective, Scope, Legal Basis and Definitions Objective

ARTICLE 5 – notwithstanding, this Regulation establishes the rules and implementation principles applicable to variations to be made to licensed human medicinal products. Scope

ARTICLE 2 – (1) This Regulation covers natural and legal persons holding marketing authorization for variations to human medicinal products licensed under the Regulation on Licensing of Human Medicinal Products published in the Official Gazette No. 31686 dated 11/12/2021. (2) Transfers of marketing authorization are outside the scope of this Regulation. Legal Basis

ARTICLE 3 – (1) This Regulation has been prepared based on the Law No. 1262 dated 14/5/1928 on Pharmaceutical and Medical Preparations, subparagraph (k) of the first paragraph of Article 3 of the Fundamental Law on Health Services No. 3359 dated 7/5/1987, and Articles 506, 507, 508 and 796 of the Presidential Decree No. 4 dated 15/7/2018 on the Organization of Ministries and Other Affiliated, Related and Associated Institutions and Organizations and Other Institutions and Organizations. Definitions

ARTICLE 4 – (1) In this Regulation; a) Urgent safety restriction: An interim change to the marketing authorization conditions arising in one or several of the product information, in particular the summary of product characteristics, indications, mode of use, dose, contraindications, warnings and withdrawal, related to the safe use of the human medicinal product and based on new information, b) Ministry: The Ministry of Health, c) Human medicinal product: 1) Any substance or combination of substances presented as having properties for treating or preventing disease in humans, or 2) Any substance or combination of substances that may be used in or administered to humans with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or making a medical diagnosis, ç) Extension application: A variation complying with the criteria set out in the list in Annex-1 and requiring a new marketing authorization application, d) Pharmacopoeia: The Turkish Pharmacopoeia (European Pharmacopoeia Adaptation), the European Pharmacopoeia, the United States Pharmacopoeia, the British Pharmacopoeia and the Japanese Pharmacopoeia; and, in cases where these pharmacopoeias are not applicable, the pharmacopoeia deemed appropriate by the Agency, e) Agency: The Turkish Medicines and Medical Devices Agency (TİTCK), f) Type IA minor variation: A variation which has only a minor impact, or no impact at all, on the quality, safety or efficacy of the human medicinal product concerned, g) Type IB minor variation: A variation which does not fall within the scope of a Type IA minor variation or a Type II major variation or an extension application, ğ) Type II major variation: A variation which is not an extension application and which may have a significant impact on the quality, safety or efficacy of the human medicinal product concerned, h) (Amended: OG-26/12/2023-32411) (1) Manufacturing site: The place where the pharmaceutical form of the human medicinal product (bulk product) is manufactured prior to its inner packaging, except in cases where human medicinal products manufactured with technologies that are not available or scarcely available in our country are evaluated by the Agency on an application basis, ı) Variation: 1) Changes in the content of the information referred to in Articles 8, 9, 10, 33, 34, 35 and 36 and Annex-1 of the Regulation on Licensing of Human Medicinal Products, or 2) In the conditions, obligations or restrictions affecting the marketing authorization and the summary of product characteristics of the human medicinal product, or, in connection with the changes made to the summary of product characteristics, in the packaging information or the package leaflet, refers to

the changes made. SECTION TWO Types and Procedures of Variations Classification of variations

ARTICLE 5 – (1) The following procedure is followed in classifying variations as Type IA minor variation, Type IB minor variation and Type II major variation: a) For variations that are not extension applications, the classification set out in Annex-2 applies. b) A variation which is not an extension application and whose classification cannot be determined in accordance with the matters specified in this Regulation, if it also cannot be determined with the aid of the guidelines prepared pursuant to Article 17 and the recommendations on unforeseen variations published on the official website of the Agency, is considered a Type IB minor variation. c) By way of exception to subparagraph (b) of the first paragraph, a variation which is not an extension application and whose classification cannot be determined in accordance with the matters specified in this Regulation, 1) If requested by the marketing authorization holder when the variation is submitted, or 2) If, pursuant to Article 9, the Agency, following the assessment of the validity of the notification, taking also into consideration the recommendations on unforeseen variations published on the official website of the Agency, concludes that the variation in question has a significant impact on the quality, efficacy or safety of the human medicinal product concerned, is considered a Type II major variation. Variations entailing the renewal of the summary of product characteristics, packaging information or package leaflet

ARTICLE 6 – (1) In cases where a variation entails the renewal of the summary of product characteristics, the packaging information or the package leaflet, such renewal is considered as part of the variation concerned. No new variation is submitted for these. Grouping of variations

ARTICLE 7 – (1) In cases where notifications or applications are made for multiple variations, a separate notification or application is submitted to the Agency for each variation requested in accordance with Articles 8, 9, 10 or 13. (2) However, in the following cases, variation applications or notifications may be grouped, provided that a fee is paid for each variation included in the group: a) Where multiple Type IA minor variations for one marketing authorization, or the same Type IA minor variation or variations for multiple marketing authorizations, are notified to the Agency simultaneously by the same marketing authorization holder, a single notification covering all these variations may be submitted, in compliance with Article 8. b) Where several variations pertaining to the same marketing authorization are submitted to the Agency simultaneously, provided that the variations concerned fall within the scope of one of the situations set out in the list in Annex-3, all these variations may be consolidated in a single notification or application. c) Where the same variations pertaining to one or multiple marketing authorizations are notified to, or applied for with, the Agency simultaneously by the same marketing authorization holder, and these do not fall within the scope of subparagraphs (a) and (b) of the second paragraph, all these variations may be consolidated in a single notification or application, provided that the Agency accepts a single notification or application. (3) For the notifications or applications referred to in subparagraphs (b) and (c) of the second paragraph: a) Where at least one of the variations is a Type IB minor variation and the other variations are minor variations, a single notification as specified in Article 9, b) Where at least one of the variations is a Type II major variation and none of the variations within its scope is an extension application, a single application as specified in Article 10, c) Where at least one of the variations is an extension application, a single application pursuant to Article 13, may be made.

Notification procedure for Type IA minor variations

ARTICLE 8 – (1) For a Type IA minor variation whose conditions are specified in the relevant guidelines prepared pursuant to Article 17, a notification containing the documents listed in Annex-4 shall be submitted by the marketing authorization holder to the Agency within twelve months following the implementation of the variation concerned. However, where there is a Type IA minor variation requiring immediate notification for the human medicinal product concerned, this notification shall be submitted to the Agency immediately after the variation concerned has been implemented. (2) Within thirty days following receipt of the notification by the Agency, the procedure specified in Article 11 shall apply. Notification procedure for Type IB minor variations

Article 9 – (1) A notification containing the documents listed in Annex-4 shall be submitted to the Agency for a Type IB minor variation, the conditions of which are set out in the relevant guidelines prepared pursuant to Article 17 by the marketing authorisation holder. Where the notification meets the requirements specified in this paragraph, the marketing authorisation holder shall be informed that a valid notification has been received by the Agency. (2) If no negative opinion is communicated to the marketing authorisation holder within thirty days after the marketing authorisation holder has been informed that a valid notification has been received by the Agency, the notification shall be deemed accepted by the Agency. Where the notification is accepted by the Agency, the procedure set out in Article 11 shall apply. (3) Where the Agency decides that the notification cannot be accepted, the marketing authorisation holder shall be informed thereof, stating the reasons for the negative opinion. Within thirty days of receiving the negative opinion, the marketing authorisation holder may submit a corrected notification to the Agency, taking into account the reasons stated in the opinion. If the marketing authorisation holder does not duly correct the notification taking into account the reasons stated in the opinion, the notification shall be deemed rejected. (4) Where a corrected notification is submitted, the Agency shall evaluate it within thirty days of receipt and the procedure set out in Article 11 shall apply. (5) Where an application for a Type IB minor variation is submitted in a grouping not containing a (repetition) or a Type II major variation, this Article shall not apply and the procedure set out in Article 10 shall apply. Where an application for a Type IB minor variation is submitted in a grouping containing a (repetition), this Article shall not apply and the procedure set out in Article 13 shall apply. Application procedure for Type II major variations

Article 10 – (1) An application containing the documents listed in Annex-4 shall be submitted to the Agency for a Type II major variation, the conditions of which are set out in the relevant guidelines prepared pursuant to Article 17 by the marketing authorisation holder. Where the application meets the requirements specified in this paragraph, the marketing authorisation holder shall be informed that a valid Type II major variation application has been received by the Agency. (2) Following the notification to the marketing authorisation holder that a valid application has been received by the Agency, an opinion shall be communicated to the marketing authorisation holder following evaluation within sixty days. This period may be shortened by the Agency in emergency situations, or extended up to ninety days for variations concerning the modification or addition of therapeutic indications as specified in Annex-5, or for the grouping of variations as specified in point (c) of the second paragraph of Article 7. (3) Within the period specified in the second paragraph, the Agency may request the marketing authorisation holder to provide supplementary information and documentation within a timeframe determined by the Agency. In this case, the procedure shall be put on hold until such supplementary information and documentation are submitted to the Agency, and the Agency may extend the period specified in the second paragraph. (4) Within thirty days following the completion of the Agency's evaluation, the procedure set out in Article 11 shall apply. (5) Where an application for a Type II major variation is submitted in a grouping containing a (repetition), this Article shall not apply and the procedure set out in Article 13 shall apply. Conclusion of the procedure

Article 11 – (1) In the cases referred to in this Article, the following shall be implemented by the Agency: a) The marketing authorisation holder shall be informed whether the variation has

been approved or rejected. b) Where the variation is rejected, the reasons for such rejection shall be communicated to the marketing authorisation holder. c) Where applicable, the marketing authorisation or authorisation certificate shall be amended by the Agency in accordance with the approved variation. ç) (Added: OG-26/12/2023-32411) Where the variations submitted to the Agency requesting the transfer of the manufacturing site of a human medicinal product from abroad to within the country or from within the country to abroad are found appropriate, a new marketing authorisation shall be issued for the human medicinal product in question. Influenza vaccines

Article 12 – (1) By way of exception to the provisions of Article 10, the procedure laid down in the second, third and fourth paragraphs shall apply to the examination of variations relating to changes made in the active substance of an influenza vaccine for the purpose of its annual update: (2) An application containing the documents listed in Annex-4, the conditions of which are set out in the relevant guidelines prepared pursuant to Article 17, shall be submitted to the Agency by the marketing authorisation holder. Where the application meets the requirements of this paragraph, the marketing authorisation holder shall be informed that a valid application has been received by the Agency. (3) The Agency shall evaluate the application submitted. Where deemed necessary, additional information and documentation may be requested from the marketing authorisation holder by the Agency in order to complete the evaluation. (4) Following the notification to the marketing authorisation holder that a valid application has been received, the evaluation shall be completed within forty-five days and the procedure set out in Article 11 shall apply. The application shall be put on hold from the date on which additional information and documentation are requested until the date on which such data are submitted to the Agency. SECTION THREE Special Procedures (Repetition)

Article 13 – (1) For a (repetition) application, a new marketing authorisation application shall be made in accordance with the Regulation on the Licensing of Human Medicinal Products. (2) A (repetition) application shall be evaluated as a new marketing authorisation application. A separate marketing authorisation shall be issued for applications found appropriate as a result of the evaluation. (3) (Added: OG-26/12/2023-32411) In cases where the cancellation of the existing marketing authorisation, to which the (repetition) application relates, is requested for the human medicinal product subject to the (repetition) application, the licensing process of the (repetition) application shall be initiated upon the official notification to the applicant of the acceptance of the preliminary evaluation of the marketing authorisation application. Pandemic situation related to influenza

Article 14 – (1) In the event of a pandemic situation related to the influenza virus being recognised by the World Health Organization or the European Union, or accepted by the Ministry, a variation of an influenza vaccine may exceptionally and temporarily be accepted by the Agency while certain non-clinical or clinical data are missing. (2) Where the variation is accepted in accordance with the first paragraph, the marketing authorisation holder shall submit the missing non-clinical and clinical data to the Agency within the timeframe determined by the Agency. Urgent safety restrictions

Article 15 – (1) In cases where human medicinal products present a risk to public health and necessitate the implementation of urgent safety restrictions, the marketing authorisation holder shall implement the urgent safety restrictions on its own initiative and shall inform the Agency immediately. If the Agency does not provide any feedback within twenty-four hours of receipt of this information, the urgent safety restrictions shall be deemed accepted, with the entire responsibility lying with the marketing authorisation holder. (2) In the event of the emergence of a situation posing a risk to public health in human medicinal products, urgent safety restrictions shall be imposed on the marketing authorisation holder by the Agency. (3) Where an urgent safety restriction is implemented by the marketing authorisation holder or imposed by the Agency, the corresponding variation application shall be submitted to the Agency by the marketing authorisation holder within fifteen days following the start date of the urgent safety restriction.

SECTION FOUR Implementation of Variations Implementation of Variations

ARTICLE 16 – (1) For Type IA minor variations, implementation may take place before the procedure referred to in Article 8 is completed. Where the notification concerning one or more Type IA minor variations is rejected, the marketing authorisation holder shall immediately cease implementing the relevant variation or variations as of the date on which the holder is notified by the Agency of the rejection of the variation pursuant to Article 11. (2) For Type IB minor variations, implementation may take place only after the marketing authorisation holder has been notified that the notification has been approved by the Agency pursuant to Article 9, or upon expiry of the period after which the notification is deemed accepted pursuant to the second paragraph of Article 9. (3) For Type II major variations, implementation may take place only after the marketing authorisation holder has been notified that the application has been approved by the Agency pursuant to Article 10. However, in pandemics and similar situations affecting public health, the Agency may introduce additional arrangements regarding the implementation of Type II major variation applications in order to facilitate public access to the medicinal product for human use. (4) A change may be implemented only after the marketing authorisation holder has been notified that a new marketing authorisation and sales permit have been granted by the Agency in accordance with the provisions of the Regulation on Licensing of Medicinal Products for Human Use. (5) Urgent safety restrictions related to safety concerns and the variations consequent thereon shall be implemented within a period jointly determined by the Agency and the marketing authorisation holder.

SECTION FIVE Miscellaneous and Final Provisions

Guidance

ARTICLE 17 – (1) Where necessary and in particular for: a) application requirements for variations and the documentation to be submitted, b) the classification of change applications by comparison with variation applications, the Agency shall publish, in the form of guidance, the general principles to be followed. (2) Where the Agency deems it necessary, it shall publish additional guidelines or communiqués concerning the implementation of this Regulation.

Reliance

ARTICLE 18 – (1) Previous assessments carried out by other medicines authorities with comparable standards or by regional or international organisations may be taken into account.

Post-approval placing on the market (Amended heading: OG-26/12/2023-32411)

ARTICLE 19 – (1) In the case of variations giving rise to a barcode change, where the marketing authorisation holder so requests; permission shall be granted, for a period of six months following the date on which the variation giving rise to the barcode change is approved, for the manufacture and placing on the market of products bearing the old barcode. The control procedures relating to the manufacturing notifications of products in this situation shall be carried out through the Pharmaceutical Track and Trace System. Such products may remain on the market until their expiry dates. (2) (Added: OG-26/12/2023-32411) In cases where, for a medicinal product for human use for which a change application has been submitted, the existing marketing authorisation subject to the change is cancelled and a new marketing authorisation is issued, permission shall be granted, for a period of six months following the date on which the authorisation is issued, for the manufacture and placing on the market of products bearing the barcode of the old authorisation with the same barcode. The control procedures relating to the manufacturing notifications of products in this situation shall be carried out through the Pharmaceutical Track and Trace System. Such products may remain on the market until their expiry dates.

Confidentiality

ARTICLE 20 – (1) In the case of variations to be made to authorised medicinal products for human use, the information submitted to the Agency by the marketing authorisation holder shall be confidential. This confidentiality shall be protected by the Agency.

Ongoing monitoring

ARTICLE 21 – (1) Where requested by the Agency, the marketing authorisation holder shall without delay provide all information requested concerning the implementation of the relevant variation.

Penal provisions

ARTICLE 22 – (1) The Turkish Penal Code No. 5237 dated 26/9/2004 and the provisions of other relevant legislation shall apply to those who fail to comply with the provisions of this Regulation. (2) In cases where the non-implementation of a variation gives rise to quality, safety and efficacy concerns for the relevant medicinal product for human use, proceedings shall be initiated in accordance with Article 22 of the Regulation on Licensing of Medicinal Products for Human Use.

Repealed Regulation

ARTICLE 23 – (1) The Regulation on Amendments to Authorised Medicinal Products for Human Use or Medicinal Products for Human Use for Which a Licensing Application Has Been Made, published in the Official Gazette No. 25823 dated 23/5/2005, has been repealed.

References

ARTICLE 24 – (1) References made to the Regulation on Amendments to Authorised Medicinal Products for Human Use or Medicinal Products for Human Use for Which a Licensing Application Has Been Made in other legislation shall be deemed to be made to this Regulation.

Status of existing applications PROVISIONAL **ARTICLE 1 –** (1) Applications concerning variations to authorised medicinal products for human use made before the entry into force of this Regulation shall be assessed in accordance with the legislative provisions in force on the date of the application, unless otherwise requested by the marketing authorisation holder.

Alignment with European Union legislation

ARTICLE 25 – (1) This Regulation has been prepared within the framework of alignment with European Union legislation, taking into consideration Commission Regulation (EC) No 1234/2008 dated 24/11/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, and Directive 2001/83/EC of the European Parliament and of the Council dated 6/11/2001 on medicinal products for human use.

Entry into force

ARTICLE 26 – (1) This Regulation shall enter into force on the date of its publication.

Execution

ARTICLE 27 – (1) The provisions of this Regulation shall be executed by the President of the Turkish Medicines and Medical Devices Agency (TİTCK).

_____ (1) By the amendment published in the Official Gazette No. 32411 dated 26/12/2023, subparagraph (h) has been added to the first paragraph of Article 4 of the Regulation following subparagraph (ğ), and the subsequent subparagraphs have been renumbered accordingly.

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