COLLEGIATE BOARD RESOLUTION – RDC No. 846 OF 6 MARCH 2024

Provides for the conditions and procedures for the marketing authorization of pre-pandemic influenza vaccines, updating to a pandemic strain, and authorization of use, commercialization, and monitoring of pandemic influenza vaccines.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 7, items III and IV, and Article 15, items III and IV of Law no. 9,782 of 26 January 1999, and item VI, paragraph 1 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Resolution, as decided upon in a meeting held on 6 March 2024, and I, Director-President, determine its publication.

CHAPTER I

OBJECTIVES AND SCOPE

Article 1. This Resolution provides for the conditions and procedures for the marketing authorization of pre-pandemic influenza vaccines, updating to a pandemic strain, and authorization of use and commercialization of pandemic influenza vaccines, and monitoring of pandemic vaccines.

Sole paragraph. Vaccines against pandemic influenza may be approved by updating the marketing authorization of pre-pandemic vaccines; however, their commercialization, distribution, and use shall only be authorized when an influenza pandemic occurs.

Article 2. This Resolution applies to companies and institutions that have the legal conditions to hold marketing authorization for medicinal products in Brazil and are authorized to manufacture or import medicinal products.

CHAPTER II

DEFINITIONS

Article 3. For the purposes of this Resolution, the following definitions are adopted:

I – pre-pandemic influenza vaccine: it is a vaccine developed and authorized before an influenza pandemic that contains the relevant strain(s) of the influenza virus with the potential to cause a pandemic, and may have its marketing authorization granted, but does not have authorization to be commercialized before a pandemic or other declared public health emergency;

II – pandemic influenza vaccine: pandemic influenza vaccines are vaccines indicated for immunization against the pandemic influenza virus and should only be used after a pandemic or other public health emergency has been recognized by health authorities;

III – influenza strains with pandemic potential: influenza virus strains with the potential to cause a pandemic or other public health emergency, with little or no circulation among humans, being poorly immunogenic and for which most of the population does not have immunity;

IV – pre-pandemic influenza vaccine marketing authorization: it is the prior marketing authorization of the pre-pandemic influenza vaccine, in which the company submits the clinical and quality data of the vaccine developed;

V – serious adverse event: any undesirable medical occurrence, at any dose, that results in death, risk of death, situations that require hospitalization or prolongation of existing hospitalization, significant or persistent disability, congenital anomaly, and clinically significant event;

VI – Equivalent Foreign Regulatory Authority (EFRA): foreign regulatory authority or international entity that has regulatory practices aligned with those of Anvisa, responsible for ensuring that the products authorized for distribution have been adequately evaluated and meet recognized standards of quality, safety, and efficacy, and which shall be considered by Anvisa in a practice of regulatory reliance.

Sole paragraph. The marketing authorization of a pre-pandemic influenza vaccine defined in item IV does not authorize the distribution, marketing, or use of this vaccine in the population before a pandemic or other declared public health emergency.

CHAPTER III

GENERAL PROVISIONS

Article 4. This Resolution allows vaccines granted marketing authorization as pre-pandemic influenza vaccines to be modified for use against pandemic influenza, updating the virus strains to the specific pandemic strain(s).

Sole paragraph. The permission provided for in the caption of this article may only be considered in specific circumstances, in which there is scientific evidence that the modified vaccine can provide protection against pandemic influenza.

Article 5. The pandemic influenza vaccine may be distributed and commercialized after approval of the authorization for use and updating to the specific strain of the virus that causes the pandemic.

Article 6. Companies that have pre-pandemic influenza vaccines under development must follow the requirements of this Resolution to manufacture batches to carry out the pre-clinical, clinical development, validation, quality control, and stability stages.

CHAPTER IV

MARKETING AUTHORIZATION OF PRE-PANDEMIC INFLUENZA VACCINE

Article 7. The marketing authorization of the pre-pandemic influenza vaccine must be supported by sufficient data from seed banks, characterization, production, quality control, stability, safety, and immunogenicity of the relevant strains, in accordance with the guidelines of the Guide for the authorization of pre-pandemic influenza vaccines and their updates issued by the European Medicines Agency (EMA), as well as applicable Guides issued by the World Health Organization (WHO).

Paragraph 1. The dossier must provide data from clinical studies conducted with the pre-pandemic preparation vaccine containing a potentially pandemic strain, which include an assessment of safety, immunogenicity, and dose-response assessment based on immunogenicity data.

Paragraph 2. Safety and immunogenicity data obtained with other potential pandemic influenza strains in addition to the one that constitutes the proposed pre-pandemic influenza vaccine may be included in the dossier as additional supporting evidence, if they are considered relevant.

Paragraph 3. Effectiveness data and complementary real-life evidence may be used to support pivotal immunogenicity and safety studies, considering the use of pandemic influenza vaccines in other localized outbreaks.

Article 8. If the strain used in the pre-pandemic influenza vaccine originates from a highly pathogenic avian influenza virus of subtypes H5, H7 or similar viruses, *in vitro* and *in vivo* tests must demonstrate the elimination of the pathogenicity of the avian influenza phenotypes.

Article 9. If the strain used in the pre-pandemic influenza vaccine is of a subtype with low pathogenicity, the tests must follow the recommendations of applicable guidelines published by the WHO or guidelines issued by EFRA defined in a specific regulation.

Paragraph 1. Antigenic characterization and analysis of genetic sequence must also be presented, in addition to safety tests.

Paragraph 2. For influenza strains obtained through reverse genetics, including the use of synthetically manufactured influenza virus gene sequences, an assessment of the result of the genetic modification and derivation in animal cells must be presented.

Article 10. The manufacturing process of the pre-pandemic influenza vaccine may be based on a process already established and related to another influenza vaccine already granted marketing authorization by Anvisa, such as that of seasonal influenza vaccines.

Sole paragraph. Even if the manufacturing process is based on another already established with another influenza vaccine already granted marketing authorization by Anvisa, the company must submit the marketing authorization of the pre-pandemic influenza vaccine with all the documents required by the current regulations, specific to the influenza strain with pandemic potential.

Article 11. The establishment of the validity period for the pre-pandemic influenza vaccine must be justified.

Paragraph 1. The stability data submitted in the marketing authorization application must correspond to at least 6 months of assessment of the active substance and the finished product.

Paragraph 2. A validity period of more than 6 months shall only be granted based on long-term stability data.

Paragraph 3. Subsequent extensions of the validity period of the active substance and the finished product must be based on long-term stability data.

Article 12. For the purposes of marketing authorization for the pre-pandemic influenza vaccine, the current scientific guidelines for influenza vaccines, non-clinical and clinical modules published by the World Health Organization (WHO) or guides on the subject published by an EFRA defined in a specific regulation may be used, where applicable.

Paragraph 1. In addition to the provisions in the caption of this article, the applicable guidelines for good manufacturing practices, established by Anvisa in a specific regulation, must be followed.

Paragraph 2. Anvisa may request additional information considering the intrinsic characteristics of the pre-pandemic influenza vaccine, the national scenario, or other technical justifications.

Article 13. The request for marketing authorization of the pre-pandemic influenza vaccine shall be analyzed in an ordinary manner, except in the event of a declared influenza pandemic, in which the analysis shall be prioritized.

Sole paragraph. The request for strain update to the pandemic strain and authorization for use shall be prioritized in the event of outbreaks or public health emergencies, provided that it is formally requested by the Ministry of Health.

Article 14. The quality documentation of the pre-pandemic influenza vaccine must comply with the requirements set forth in Resolution RDC No. 55 of 16 December 2010 and its updates.

Sole paragraph. All companies involved in manufacturing must comply with good manufacturing practices and present the Good Manufacturing Practices Certificate (CBPF, in Portuguese) issued by Anvisa.

Article 15. The non-clinical documentation for the pre-pandemic influenza vaccine must provide the inputs provided for in one of the following guides and their updates:

I – WHO guidelines on non-clinical evaluation of vaccines, WHO Technical Report Series No. 927, Annex 1, and WHO Guidelines on the non-clinical evaluation of vaccine adjuvants and adjuvanted vaccines; or

II – EMA/CHMP/VWP/457259/2014 – Committee for Medicinal Products for Human Use – Guideline on Influenza Vaccines Non-clinical and Clinical Module; or

III – current guides on the subject published by an EFRA defined in a specific regulation.

Article 16. The clinical documentation for the pre-pandemic influenza vaccine must provide the inputs provided for in one of the following guides and their updates:

I – WHO Guidelines on clinical evaluation of vaccines: regulatory expectations; or

II – EMA/CHMP/VWP/457259/2014 – Committee for Medicinal Products for Human Use – Guideline on Influenza Vaccines Non-clinical and Clinical Module; or

III – current guides on the subject published by an EFRA defined in a specific regulation.

Article 17. The marketing authorization of the pre-pandemic influenza vaccine may be conditionally approved, by means of a Term of Commitment, for subsequent completion of data and evidence, at the discretion of Anvisa.

Sole paragraph. The company must provide an execution schedule for the additional data to be generated for the pre-pandemic influenza vaccine, accompanied by the pertinent risk analyses.

CHAPTER V

UPDATING THE PRE-PANDEMIC INFLUENZA VACCINE STRAIN TO THE PANDEMIC INFLUENZA VACCINE AND AUTHORIZATION OF USE OF THE PANDEMIC VACCINE

Article 18. In the event of a pandemic or other public health emergency caused by the influenza virus, declared by the World Health Organization or the Brazilian Ministry of Health, the company must submit a formal request for updating to the pandemic strain and authorization of use of the pandemic influenza vaccine.

Paragraph 1. The pandemic influenza vaccine object of the authorization request must already contain the updated strain of the influenza virus that is causing the public health emergency.

Paragraph 2. The request for strain update and authorization for use must be accompanied by a document issued by the Ministry of Health indicating the need for the pandemic influenza vaccine to support the vaccination program in Brazil.

Paragraph 3. The request for strain update and authorization for use shall be considered a priority and shall meet the deadlines set forth in RDC 204/2017 and its updates.

Article 19. The strain update and authorization for use of the pre-pandemic influenza vaccine may be conditionally approved, through a Term of Commitment, for subsequent completion of data and evidence, at the discretion of Anvisa.

Paragraph 1. The company must provide an execution schedule for the additional data to be generated for the pandemic influenza vaccine, accompanied by the pertinent risk analyses.

Paragraph 2. The conditional approval shall be revoked if the benefit-risk ratio proves to be unfavorable throughout the evaluation of the pandemic vaccine data.

Article 20. The request for updating the strain and authorization for use of the pandemic influenza vaccine must be based on data obtained from a pre-pandemic influenza vaccine already granted marketing authorization, regarding the quantity of antigen, excipients, adjuvants in the formulation, and production process.

Article 21. The company holding the marketing authorization of the pre-pandemic influenza vaccine must file the request for updating the strain and authorization for use, with a specific subject code, together with the pre-pandemic influenza vaccine marketing authorization process, containing the following documents and information, considered essential for updating the strain of the pre-pandemic influenza vaccine to the pandemic influenza vaccine:

I – declaration of a public health emergency by the World Health Organization or the Brazilian Ministry of Health;

II – statement by the Brazilian Ministry of Health indicating the need for the pandemic influenza vaccine to support the vaccination program in Brazil;

III – identification of the strain that gave rise to the pandemic;

IV – updated leaflet and labeling models with information related to the pandemic strain;

V – information on the establishment of the pandemic influenza vaccine seed batches: characterization, history of the seed batch, number of passages;

VI – information on quality control, including information on tests performed on the seed batch, if the pre-pandemic influenza vaccine strain was developed internally by the manufacturer;

VII – evaluation of the cell substrate in relation to relevant adventitious agents, such as contaminants originated from culture cells and those that can be inserted into the product through reagents used during the establishment of cell banks;

VIII – information on the yield of the HA antigen in the harvesting stage;

IX – validation of critical stages of the process that have been shown to be strain-specific;

X – studies to characterize the active substance, containing at least the comparability of critical quality attributes, accompanied by a discussion on safety and immunogenicity, if any difference is detected;

XI – information on the quality of the adjuvants and their development, if different from that used in the pre-pandemic influenza vaccine;

XII – stability data of the active substance and finished product available for the pandemic influenza vaccine;

XIII – clinical data regarding the immunogenicity and safety of the influenza vaccine with the pandemic strain;

XIV – observational studies for additional assessment of safety and immunogenicity;

XV – risk management plan for monitoring the pandemic vaccine.

Paragraph 1. The company must supplement the quality information, non-clinical and clinical, as provided for in Article 7 to Article 16, throughout the development of the pandemic vaccine.

Paragraph 2. The company must discuss and agree with Anvisa the design and conduct of the effectiveness study of the pandemic vaccine, during the analysis and before the approval of the update request for the pandemic vaccine.

Paragraph 3. The company must discuss and agree with Anvisa the plans for enhanced safety surveillance to be carried out during the pandemic period.

Paragraph 4. The requirements listed in the caption of this article are the minimum information considered essential for updating the pre-pandemic influenza vaccine strain to the pandemic influenza vaccine.

Article 22. If the pandemic strain is the same as the one that supported the marketing authorization of the pre-pandemic vaccine, the request for updating the strain and authorization for use must contain only the documents and information established in items I, II, III, and XIV of Article 21.

Article 23. The first three batches of bulk product derived from a new seed bank must be tested for the presence and type of neuroaminidase (NA) antigen.

Sole paragraph. When the information that is not yet available refers to materials that pose a potential safety risk, a risk assessment must be presented, considering the control strategy applied and the characteristics of the production process.

Article 24. The validity period of the pandemic influenza vaccine may be based on long-term and accelerated data, using information from the pre-pandemic influenza vaccine.

Paragraph 1. The stability study with the pandemic influenza vaccine must be completed and the data confirming its validity period must be sent to Anvisa upon its completion or at the intervals agreed with the Agency.

Paragraph 2. Out-of-specification results or significant trends in any quality attribute of the pandemic influenza vaccine must be reported to Anvisa.

Article 25. After approval of the strain update and authorization for use of the pandemic influenza vaccine, the company may begin distributing and commercializing the vaccine to supply doses to the Brazilian Ministry of Health, with this formulation then being identified as the pandemic influenza vaccine.

Article 26. The pandemic vaccine shall be intended exclusively for use in the public health program of the Brazilian Ministry of Health.

Article 27. Anvisa may, at any time, request specific studies, data, and additional information that it deems necessary to prove that the benefit of using the pandemic vaccine remains favorable in relation to the risks.

Article 28. The manufacturer must have a good manufacturing practices certification issued by Anvisa to produce the pandemic vaccine.

CHAPTER VI

MONITORING

Article 29. The pandemic influenza vaccine granted marketing authorization in accordance with this Resolution has the same obligations regarding compliance with the determinations provided for in Collegiate Board Resolution – RDC No. 406 of 22 July 2020 and its updates.

Paragraph 1. Serious adverse events related to the pandemic vaccine granted marketing authorization in accordance with this Resolution must be reported to Anvisa by the marketing authorization holder within 72 (seventy-two) hours from the date of their knowledge, through the electronic notification system made available by Anvisa.

Article 30. Additional information must be collected from observational studies that can be conducted to expand the safety and immunogenicity database.

Article 31. It is recommended that additional data be collected from populations that were studied to a lesser extent in clinical trials prior to the marketing authorization of the pre-pandemic influenza vaccine.

Article 32. Studies on the effectiveness of the vaccine in Brazil must be conducted, with an assessment of the population included in the therapeutic indication.

CHAPTER VII

FINAL AND TRANSITIONAL PROVISIONS

Article 33. Batches of pandemic influenza vaccines, after authorization for use with an update of the pandemic strain, may only be released for use in the population after the batch analysis report is issued by the National Institute for Quality Control in Health (INCQS, in Portuguese) after carrying out the assessments provided for in Collegiate Board Resolution – RDC No. 73 of 21 October 2008 and its updates.

Article 34. The marketing authorization of the pre-pandemic influenza vaccine shall be valid for the ordinary period of a medicinal product, in accordance with Collegiate Board Resolution – RDC No. 317 of 22 October 2019 and its updates.

Paragraph 1. The pre-pandemic influenza vaccine granted marketing authorization may not be commercialized, distributed, and used before the update of the strain and authorization for use issued by Anvisa for the pandemic influenza vaccine.

Paragraph 2. The update of the strain and authorization for use granted for a pandemic vaccine may be modified, suspended, or revoked by Anvisa at any time, in a substantiated manner, for technical and scientific reasons or based on information from the control and monitoring of the vaccine.

Article 35. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, under Law No. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 36. This Resolution shall come into force on 15 March 2024.

ANTONIO BARRA TORRES

Director-President