COLLEGIATE BOARD RESOLUTION – RDC No. 205 OF 28 DECEMBER 2017

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Establishes a special procedure for the approval of clinical trials, good manufacturing practices certification, and marketing authorization for new medicinal products for treatment, diagnosis, or prevention of rare diseases.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, combined with Article 7, items III and IV, of Law no. 9782 of 26 January 1999, and Article 53, item V, paragraphs 1 and 3, of the Internal Regulation approved by Annex I of Collegiate Board Resolution – RDC no. 61 of 3 February 2016, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 12 December 2017, and I, the Director-President, determine its publication:

CHAPTER I

INITIAL PROVISIONS

Article 1. This Resolution approves the special procedure for:

I – the approval of clinical trials to be conducted in Brazil for the assessment of medicinal products for rare diseases;

II – good manufacturing practices certification applicable to medicinal products for rare diseases; and

III – marketing authorization for new medicinal products for rare diseases.

Article 2. This Resolution is applied to new medicinal products for rare diseases.

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

I – rare disease: disease that affects up to sixty-five in one hundred thousand people, according to the definition established by the Brazilian Policy of Full Attention to People with Rare Diseases, based on official Brazilian data or, when inexistent, on data published in technical-scientific documentation;

II – new medicinal product: medicinal product with an unprecedented active pharmaceutical ingredient (API) in Brazil for the specific rare disease;

III – serious debilitating condition: disease or condition associated to irreversible morbidity or to the high death probability, unless the course of the disease is interrupted; and

IV – technical-scientific documentation: documentation based on bibliographic references, indexed scientific publication, of Brazilian or international origin, and technical publication, as the ones issued by health and governmental authorities.

CHAPTER II

GENERAL PROVISIONS

Article 4. For this Resolution's criteria to be used, the application for approval of clinical trials, good manufacturing practices certification, and marketing authorization for a new medicinal product must refer to a medicinal product for a rare disease.

Sole paragraph. A medicinal product for a rare disease shall be considered so if it has the objective of treating, diagnosing, or preventing a rare disease, in addition to:

I – being used for a serious debilitating condition; and

II – being intended to alter, in a clinically significant way, the evolution of the disease, or enable remission of the disease.

Article 5. At the moment of submission of the application for approval of clinical trials and for the marketing authorization for a new medicinal product, the company must inform if the application refers to a medicinal product for a rare disease.

Article 6. For clinical trials to be conducted in Brazil, when the application subject refers to a Medicinal Product Clinical Development Dossier (DDCM, in Portuguese), the analysis is applied only to the applications submitted and analyzed together with the initial application, in accordance with the criteria in this Resolution.

Sole paragraph. Specific dossiers of clinical trials and substantial alterations made by inclusion of protocol, subsequently linked to a DDCM, shall be assessed in accordance with this Resolution as long as the company informs if the application refers to a medicinal product for a rare disease at the moment of the submission.

Article 7. The applications for approval of clinical trials and for the marketing authorization for new medicinal products referring to medicinal products for rare diseases must have the following additional documentation:

I – description of the rare disease which the medicinal product will be indicated for;

II – relevance of the medicinal product for the treatment, diagnosis, or prevention of the disease;

III – worldwide and Brazilian data on prevalence and incidence of the rare disease which the medicinal product will be indicated for; and

IV – document confirming the designation of the medicinal product for a rare disease issued by another regulatory authority, when available.

Article 8. In case there is no confirmation, during the technical analysis of the applications for approval of clinical trials and for the marketing authorization for a new medicinal product, that the application refers to a medicinal product for a rare disease, the application shall be rejected.

Section I

Approval of clinical trials to be conducted in Brazil

Article 9. The submission of a medicinal product clinical development dossier (DDCM), specific clinical trial dossier, or substantial alterations made by inclusion of protocol, must be made according to the specific legislation referring to the conduction of such clinical trials with medicinal products in Brazil, in addition to the documentation described in Article 7.

Sole paragraph. The approval of clinical trials to be conducted in Brazil with a medicinal product for a rare disease may be granted without presenting a consubstantiated report issued by the Research Ethics Committee (CEP, in Portuguese).

Article 10. The procedures below must be followed for the purposes of approval of clinical trials to be conducted in Brazil with medicinal products for rare diseases:

I – request by the interested party for a pre-submission meeting to present the DDCM, a specific clinical trial dossier, or substantial alterations by inclusion of protocol;

II – pre-submission meeting to present the DDCM, a specific clinical trial dossier, or substantial alterations by inclusion of protocol, in up to sixty days after the request by the interested party;

III – submission of DDCM, a specific clinical trial dossier, or substantial alterations by inclusion of protocol, by the interested party, using a specific subject code;

IV – assessment of the DDCM, a specific clinical trial dossier, or substantial alterations by inclusion of protocol, by Anvisa, in up to thirty days after the submission, issuing either a demand notification or a conclusion manifestation;

V – meeting, if considered necessary by the interested party, to discuss the demands;

VI – compliance with the demands by the interested party in up to thirty days after the notification is read; and

VII – assessment of the compliance with the demands, by Anvisa, in up to thirty days after the submission at the agency.

Article 11. The secondary applications, referring to a DDCM, a specific clinical trial dossier, or substantial alterations by inclusion of protocol, assessed in accordance with the criteria in this Resolution, shall have the same treatment.

Section II

Good Manufacturing Practices Certification

Article 12. The request for the good manufacturing practices certification must be made in compliance with the specific legislation referring to the procedures for granting the good manufacturing practices certification.

Article 13. The procedures below must be followed for the purposes of good manufacturing practices certification:

I – request for the good manufacturing practices certification for the plants where the medicinal product will be produced, by the interested party; and

II – publication of the decision regarding the good manufacturing practices certification, by Anvisa, in up to one hundred and twenty days after the certification request was submitted.

Section III

Marketing Authorization

Article 14. The application for the marketing authorization for a new medicinal product for a rare disease must be made in compliance with the specific legislation for each regulatory category, in addition to the documentation described in Article 7.

Paragraph 1. In the case of medicinal products already authorized in other countries, a technical assessment report of the medicinal product must be presented, issued by the respective regulatory authorities, when available.

Paragraph 2. The submission of the marketing authorization application may be accepted if the company presents a confirmation of inspection request for the purposes of good manufacturing practices certification.

Paragraph 3. Upon the submission of the marketing authorization application, an ongoing long duration stability study may be accepted, being conducted in accordance with the temperature and humidity conditions required by specific legislation, with results available up to the date of submission.

Paragraph 4. Safety and efficacy reports may be accepted, together with completed phase II studies and ongoing phase III studies, or without phase III clinical studies, when their conduction is not feasible.

Paragraph 5. In the case of imported medicinal products, quality control suppression is permitted in Brazil, as long as quality control is carried out by the medicinal product manufacturer, and the company presents a summary report on the transportation system operation qualification.

Paragraph 6. The marketing authorization application may be submitted in accordance with the Common Technical Document (CTD) format, provided for in the M4 guide issued by the International Conference on Harmonization (ICH).

Article 15. The presentation of data complementation and additional confirmation documents after the marketing authorization grant is permitted, by means of a term of commitment signed between Anvisa and the company applying for the marketing authorization.

Sole paragraph. Failure to comply with the commitments signed for may lead to cancel the medicinal product marketing authorization.

Article 16. In the cases where the company applying for the marketing authorization does not have the full clinical development of the medicinal product for a rare disease with a new active pharmaceutical ingredient (API) in Brazil, a clinical report may be presented, including:

I – safety and efficacy data based on bibliographic references from an indexed scientific publication, of Brazilian or international origin;

II – *in vitro* or *in vivo* comparability studies using an international comparator medicinal product;

III – relative bioavailability/ bioequivalence studies using an international comparator medicinal product, when applicable;

IV – leaflet and public assessment report of the international comparator medicinal product issued by a regulatory authority;

V – pharmacovigilance plan or risk minimization plan, when applicable, in accordance with specific legislation; and

VI – updated pharmacovigilance report of the medicinal product, in case of medicinal products commercialized in other countries.

Paragraph 1. For the purposes of marketing authorization in the condition provided for in the caption of this Article, Anvisa may allow the use of an international comparator medicinal product authorized by another regulatory authority when:

I – there is an agreement signed with Anvisa, and the health measures taken by Anvisa and the regulatory authority are similar; and

II – the marketing authorization of the comparator medicinal product has been valid for at least ten years in the regulatory authority and the medicinal product is commercialized.

Paragraph 2. Before the marketing authorization application is submitted, the company must make a consultation with Anvisa about the international comparator medicinal product proposed to be used.

Paragraph 3. The leaflet of the medicinal product to be authorized by Anvisa shall have the same indications, administration routes, and posology of the international comparator medicinal product's leaflet, and it may differ in complementary safety information only.

Paragraph 4. The medicinal product authorized in the terms of the caption of this Article cannot be elected as a reference medicinal product.

Paragraph 5. The provisions in the caption of this Article are not applied to biological products.

Article 17. Anvisa may allow the use of an international comparator medicinal product authorized by another regulatory authority, in the terms provided for in Paragraph 1 of Article 16, in case of marketing authorization application for a medicinal product for a rare disease with the same APIs of a medicinal product already authorized.

Sole paragraph. The medicinal products included in the situation described in the caption of this Article shall only follow the criteria in this Resolution regarding the possibility of using an international comparator medicinal product, and the other special procedures are not applied.

Article 18. The procedures below must be followed for the purposes of marketing authorization for a new medicinal product for a rare disease:

I – request by the interested party for a pre-submission meeting to present the product;

II – pre-submission meeting to present the product, in up to sixty days after the request by the interested party;

III – submission of the marketing authorization application by the interested party, using a specific subject code, in up to thirty days after the pre-submission meeting;

IV – assessment of the medicinal product marketing authorization application by Anvisa, in up to sixty days after the submission, issuing a demand notification or a conclusion manifestation;

V – meeting, if considered necessary by the interested party, to discuss the demands;

VI – compliance with the demands by the interested party in up to thirty days after the notification is read; and

VII – assessment of the compliance with the demands, by Anvisa, in up to forty-five days after the submission at the agency.

Paragraph 1. If the pre-submission meeting is not requested, in the terms of item I of the caption of this Article, the marketing authorization application shall not be analyzed in accordance with this Resolution.

Paragraph 2. In the case of medicinal products developed in Brazil, the pre-submission meeting may be requested at any time, as long as the marketing authorization has not been applied for at another regulatory authority.

Paragraph 3. In the case of imported medicinal products, the pre-submission meeting must be requested in up to sixty days after the first marketing authorization is applied for at another regulatory authority, unless it is not attributable to the interested company.

Paragraph 4. In the cases where the marketing authorizations for medicinal products for rare diseases have been applied for, or if the medicinal products have already been authorized by other health authorities before this Resolution is published, the pre-submission meetings provided for in item I of the caption of this Article may be requested at any time.

CHAPTER II

FINAL AND TRANSITIONAL PROVISIONS

Article 19. The companies that submit an application for the marketing authorization for new medicinal products according to the criteria in this Resolution must present a maximum price definition dossier together with the marketing authorization application.

Article 20. The medicinal products authorized by means of the criteria in this Resolution shall have a period of up to three hundred and sixty-five days to be commercialized, counting from the date the marketing authorization is published.

Article 21. The provisions in Article 2 of Collegiate Board Resolution – RDC no. 20 of 10 April 2013 are not applied to applications for the marketing authorization for new medicinal products for rare diseases.

Article 22. The letter “e” of Item IV or Article 3, and the letter “e” of Item VIII of Article 38 of Collegiate Board Resolution – RDC no. 9 of 20 February 2015 are hereby revoked.

Article 23. Paragraph 2 of Article 47 of Collegiate Board Resolution – RDC no. 9 of 2015 shall be replaced by the following:

“Article 47. ……..

…… Paragraph 2. The application for substantial amendments must contain the new protocol.

……” (New Wording)

Article 24. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, pursuant to Law no. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 25. This Resolution enters into force 60 (sixty) days after the date of its publication.

JARBAS BARBOSA DA SILVA JR.