COLLEGIATE BOARD RESOLUTION – RDC NO. 412 OF 20 AUGUST 2020

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Establishes the requirements and conditions for the conduction of stability studies for the purposes of marketing authorization and post-marketing authorization alterations of biological products and makes other provisions.

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, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and item V, paragraphs 1 and 3 of Article 53 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 255 of 10 December 2018, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 18 August 2020, and I, Acting Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Article 1. This Resolution establishes the requirements and conditions for the conduction of stability studies for the purposes of marketing authorization and post-marketing authorization alterations of products granted marketing authorization by Anvisa as biological products, as defined in Collegiate Board Resolution – RDC No. 55 of 16 December 2010 and its updates.

Article 2. For the purposes of this Resolution, the following definitions are adopted:

I – bracketing: design of the stability program in which samples of the extremes of certain factors are tested, assuming that the stability of any intermediate presentation is represented by the extremes tested;

II – primary packaging: packaging component that comes or may come into direct contact with the pharmaceutical form of the product (for example, vial, pre-filled syringe) or components that contribute towards the integrity of the container or its closing system for a sterile product;

III – temperature cycling study: study carried out to evaluate the effect of permanence of the product in conditions other than those defined for transportation or storage;

IV – accelerated stability study: study designed to increase the rate of chemical degradation or physical alteration of an active substance or finished product through storage under critical conditions;

V – follow-up stability study: stability study carried out to ensure that the pharmaceutical product maintains its physical, chemical, biological, and microbiological characteristics, in accordance with the results obtained in long-term stability studies;

VI – long-term stability study: stability study under the recommended storage conditions, considering the proposed shelf life;

VII – in-use stability study: stability study carried out simulating real conditions of use of the product to ensure that its quality is maintained under the storage conditions and period recommended by the manufacturer;

VIII – stress study: study carried out to assess stability under more severe conditions than those used in the accelerated stability study;

IX – photostability study: stability study carried out to evaluate the effect of exposure to light on the active substance or on the finished product;

X – Product Alteration History: documentation that records information about the current status and the alterations occurred in the product marketing authorization in a period of 12 (twelve) months;

XI – intermediate product: material generated during the manufacturing steps of the active substance or biological product that will be subjected to further processing;

XII – commercial batch: batch of active substance, intermediate product, or finished product manufactured on a commercial scale, using equipment and manufacturing plant, as specified in the submission of the marketing authorization dossier or post-marketing authorization alteration;

XIII – batch on a pilot scale: batch of active substance, intermediate product, or finished product manufactured through a process completely representative of that applied to a commercial batch, where in the case of the active substance, the methods of cell expansion, collection, and purification must be identical to the commercial scale, except for scale size;

XIV – matrixing: design of a stability program in which subgroups of a total of available samples are tested alternately and at a specific frequency for all combination factors, assuming that the stability of each subgroup of the sample represents the stability of all samples in a given time interval;

XV – reference standard: suitably characterized material used as a reference to assess batches of active substance, intermediate products, and finished product;

XVI – shelf life: period in which the active substance, intermediate products, or the finished product are expected to remain in accordance with the approved specifications, provided they are stored under the conditions defined by the manufacturer;

XVII – degradation products: molecules resulting from alterations in the active substance over time;

XVIII – diluted product: product in liquid form after adding the diluent for administration to the user;

XIX – reconstituted product: liquid product obtained by adding diluent to the finished product presented in powder form;

XX – finished product: product in the pharmaceutical form and in the primary packaging in which it will be commercialized, which may be in the secondary packaging; and

XXI – active substance: active biological pharmaceutical ingredient, which may be subsequently formulated for the manufacture of a certain biological product.

CHAPTER II

GENERAL PROVISIONS

Article 3. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Harmonized tripartite guideline. Quality of biotechnological products: stability testing of biotechnological/ biological products – Q5C, of 30 November 1995, and its updates must be used to support the stability assessment of biological products, depending on the case and the nature of the product.

Paragraph 1. The following guidelines must be used in addition to the guideline indicated in the caption of this article to support the stability assessment, depending on the case and nature of the product:

I – ICH Harmonized tripartite guideline. Stability testing of new drug substances and products – Q1A(R2) of 6 February 2003 and its updates;

II – ICH Harmonized tripartite guideline. Stability testing: photostability testing of new drug substances and products – Q1B of 6 November 1996 and its updates;

III – ICH Harmonized tripartite guideline. Bracketing and matrixing designs for stability testing of new drug substances and products – Q1D of 7 February 2002 and its updates;

IV – ICH Harmonized tripartite guideline. Evaluation for Stability Data – Q1E of 6 November 2003 and its updates;

V – ICH Harmonized tripartite guideline. Specifications: test procedures and acceptance criteria for biotechnological/ biological products – Q6B of 10 March 1999 and its updates;

VI – ICH Harmonized tripartite guideline. Validation of analytical procedures: text and methodology – Q2(R1) of 27 October 1994 and its updates; and

VII – Committee for Proprietary Medicinal Products (CPMP). Note for guidance on in-use stability testing of human medicinal products, dated 1 March 2001, and its updates.

Paragraph 2. Alternative approaches may be accepted on an exceptional basis and upon presentation of a technical justification for assessment by Anvisa.

Article 4. For the purposes of marketing authorization, stability reports must be accompanied by detailed study protocols.

Paragraph 1. The protocol referred to in the caption of this article must include stability studies of the active substance, the intermediate product, the finished product, and the diluent, when applicable.

Paragraph 2. Alterations to the stability study protocol approved in the marketing authorization must be requested through a post-marketing authorization alteration petition, in accordance with Collegiate Board Resolution – RDC No. 413 of 20 August 2020 and its updates.

Article 5. The stability report must contain the following information:

I – manufacturing date and number of batches;

II – description of the storage container and/ or primary packaging;

III – manufacturing sites of the active substance, intermediate product, diluent, and finished product are, as the case may be;

IV – batch size;

V – tests and specifications;

VI – test times and intervals;

VII – conditions for carrying out the study;

VIII – storage position of the container (for example, horizontal, vertical, inverted) when the contact of the product with the closing system affects the stability of the product; and

IX – results and discussion.

Article 6. The manufacturer must propose a profile indicative of stability that guarantees that variations in the identity, purity, and potency of the product are detected.

Article 7. The limits of impurities and degradation must be established based on data obtained from batches used in pre-clinical and clinical studies and validation of the manufacturing process.

Article 8. The product evaluated in the long-term stability study must maintain its specifications within the limits established in the stability protocol throughout the proposed shelf life.

Sole paragraph. Out-of-specification results must be investigated and justified and may be accepted as long as it is demonstrated that they are not related to the lack of stability of the product.

Article 9. The storage containers used during the stability studies must be the same or representative of the containers used in the commercial batches.

Article 10. The quality of the batches evaluated in the stability program must be representative of the quality of the batches used in pre-clinical and clinical studies and the quality of the material produced on a commercial scale.

Article 11. When a product is manufactured in presentations that differ in filling volume, number of units and/ or mass, samples used in the stability study may be selected based on a matrixing or bracketing system, in accordance with the conditions provided for in ICH Q1D and ICH Q5C guidelines and their updates.

Paragraph 1. The studies submitted for evaluation must be representative of the stability of all pharmaceutical forms, presentations, packaging, and concentrations.

Paragraph 2. Matrixing must not be applied to samples with differences that may affect stability, such as different amounts of active substance in the pharmaceutical form and different packages, when it cannot be confirmed that the products respond similarly under storage conditions.

Article 12. If the long-term stability studies carried out under the conditions established in this Resolution prove, at any time, a validity period lower than that approved in the product

marketing authorization, the company must immediately inform the competent area of Anvisa about the fact and submit the post-marketing authorization alteration to reduce the validity period in accordance with the data obtained.

Article 13. For all post-marketing authorization alterations that require stability studies of the active substance, intermediate product, finished product, diluent, and/ or reference standard, the provisions of Collegiate Board Resolution – RDC No. 413 of 20 August 2020 and its updates must be complied with.

CHAPTER III

STABILITY STUDIES

Section I

Accelerated Stability Study

Article 14. In the accelerated stability study, there must be at least 3 (three) time points of analysis for each batch, including the initial and final times of the study.

Article 15. The temperature and humidity conditions for the accelerated stability studies of the active substance and intermediate products, for the finished product, and for water-based products, are presented in Annexes I, II, and III of this Resolution, respectively.

Sole paragraph. The manufacturer may define alternative conditions based on the characteristics of the product, in order to provide relevant data about its stability profile.

Section II

Long Term Stability Study

Article 16. For products with a shelf life longer than 12 (twelve) months, the long-term stability study tests must be conducted at least every 3 (three) months in the first year of storage, every 6 (six) months in the second year, and annually thereafter.

Article 17. For products with a shelf life equal to or shorter than 12 (twelve) months, tests must be conducted monthly during the first 3 (three) months and at intervals of 3 (three) months thereafter.

Article 18. The intervals established in articles 16 and 17 of this Resolution may be altered or suppressed through a post-marketing authorization alteration petition, based on data that indicate that the assessment of the stability of the product is not compromised.

Article 19. The batches included in the long-term stability study must be tested at least until the last month of the product's shelf life.

Article 20. The temperature and humidity conditions for the long-term stability studies of the active substance and intermediate products, for the finished product, and for water-based products, are presented in Annexes I, II, and III of this Resolution, respectively.

Section III

Stability Study under Stress Condition

Article 21. It is recommended that the company evaluate the possible impact of exposure to extreme conditions in a stress study with at least one batch of active substance and finished product.

Sole paragraph. The conditions for conducting the stress study must be defined and technically justified on a case-by-case basis by the manufacturer.

Section IV

Photostability Study

Article 22. The photostability study must be conducted in accordance with ICH Q1B guideline and its updates.

Sole paragraph. Alternative conditions may be used, provided they are technically justified.

Section V

Stability Study of In-use, Reconstituted, or Diluted Product

Article 23. The stability of in-use, reconstituted, and/ or diluted finished product must be demonstrated at least under the specified conditions and for the storage period described on the label, package insert, and/ or carton, as applicable.

Article 24. The study must evaluate the properties of the product susceptible to alterations during use.

Article 25. The stability study of in-use, reconstituted, and/ or diluted product must be carried out with at least 2 (two) batches of the finished product.

Sole paragraph. It is recommended to carry out the tests on at least one batch at the end of the expiration date.

Article 26. A study to evaluate the compatibility of the product with the intravenous diluent(s), bags, and infusion lines, when appropriate, must be presented.

Article 27. For multidose packaging, the company must demonstrate that the packaging can withstand the conditions of repeated insertions of the needle, simulating the use of the product, so that the microbiological parameters, potency, purity, and other quality attributes remain unaltered for the maximum period specified in the instructions for use.

Paragraph 1. The study must be conducted in accordance with the Committee for Proprietary Medicinal Products (CPMP) note. Note for guidance on in-use stability testing of human medicinal products, dated 1 March 2001, and its updates.

Paragraph 2. Alternative conditions may be used, provided they are technically justified.

Section VI

Temperature Cycling Study

Article 28. In case of temperature deviation during transportation or storage of the biological product, a temperature cycling study must be presented for the purpose of releasing the cargo.

Paragraph 1. The temperature cycling study must be carried out with at least 1 (one) batch representative of the commercial scale.

Paragraph 2. The cycling study must be representative of the temperature deviation that occurred during transportation or storage.

Paragraph 3. The samples subjected to temperature cycles must be kept in long-term storage conditions and evaluated until the end of the product's shelf life.

Paragraph 4. Exceptionally, in the case of a cycling study in progress, partial data must be presented accompanied by a technical justification that supports the verified deviation.

CHAPTER IV

STABILITY STUDIES FOR THE PURPOSES OF MARKETING AUTHORIZATION

Section I

Active Substance and Intermediate Products

Article 29. If the active substance and/ or intermediate products remain stored in a certain condition before starting the next stage, the company must provide accelerated and long-term stability data for at least 3 (three) batches on a pilot or commercial scale.

Article 30. The shelf life of the active substance and intermediate products shall be defined based on actual data from the long-term stability study.

Paragraph 1. Accelerated stability studies are not sufficient to determine the expiration date.

Paragraph 2. In exceptional situations, in the case of non-protein/ non-polypeptide molecules, except for active substances and intermediate products of vaccines, the determination of the expiration date may be based on ICH Q1A (R2) and Q1E guidelines and their updates.

Article 31. When data from batches of active substance and intermediate products manufactured on a pilot scale are used for the purposes of determining the expiration date for marketing authorization, the holder must submit a commitment that the long-term stability data of the first 3 (three) batches produced on a commercial scale will be presented to Anvisa.

Sole paragraph. The final report of the long-term stability studies of at least 3 (three) batches produced on a commercial scale must be sent to Anvisa as an integral part of the next Product Alteration History after the completion of the study.

Section II

Finished Product

Article 32. The company must provide accelerated and long-term stability data for at least 3 (three) batches on a pilot or commercial scale.

Article 33. The shelf life of the finished product shall be defined based on real data from the long-term stability study of at least 3 (three) batches on a pilot or commercial scale.

Paragraph 1. Accelerated stability studies are not sufficient to determine the expiration date.

Paragraph 2. If the 3 (three) batches referred to in the caption of this article are not included simultaneously in the stability study, the shelf life of the finished product shall be defined based on real data from the batch with the shortest follow-up time.

Paragraph 3. In exceptional situations, in the case of non-protein/ non-polypeptide molecules, except for vaccines, the determination of the expiration date may be based on ICH Q1A (R2) and Q1E guidelines and their updates.

Article 34. When data from batches of a finished product manufactured on a pilot scale are used for the purposes of marketing authorization, the holder must submit a commitment that the long-term stability data of the first 3 (three) batches produced on a commercial scale will be presented to Anvisa.

Sole paragraph. The final report of the long-term stability studies of at least 3 (three) batches produced on a commercial scale must be sent to Anvisa as an integral part of the next Product Alteration History after the completion of the study.

Article 35. The batches of finished product used in stability studies should preferably be manufactured with different batches of active substance.

Sole paragraph. If it is impossible to present stability data of batches of the finished product manufactured with different batches of active substance in the marketing authorization submission, the company must carry out such evaluation in the follow-up stability study.

Article 36. It is recommended to use batches of active substance and intermediate products of different storage periods for the manufacture of the finished product to evaluate the cumulative stability of the product.

Article 37. When product interactions with the primary packaging and closure system cannot be excluded in liquid products other than sealed ampoules, stability studies must include samples held in an inverted or horizontal position (that is, in contact with the closure) as well as in an upright position.

Article 38. Stability data obtained with all types of primary packaging and closure systems used for the finished product must be presented.

Article 39. The storage temperature and humidity for finished product stability studies must satisfy the conditions indicated in Annex II.

Paragraph 1. For finished products packaged in impermeable containers, stability studies may be carried out under any condition of relative humidity.

Paragraph 2. For water-based products packaged in semipermeable containers, stability studies must assess the possibility of water loss, in this case, studies must be carried out under conditions of low relative humidity, as described in Annex III.

Article 40. If the presentation of the product consists of a solution for reconstitution or dilution or an auxiliary product, in its own packaging, the company must present the accelerated and long-term stability study for 3 (three) batches of the product.

Sole paragraph. If the solution for reconstitution or dilution or auxiliary product has a current marketing authorization by Anvisa, the presentation of these studies is waived by indicating the corresponding marketing authorization number.

Article 41. In addition to the accelerated and long-term stability studies, for the purposes of marketing authorization, stability studies of in-use, reconstituted, or diluted product and photostability studies, when applicable, as described in Chapter III of this Resolution are required.

Section III

Reference Standards

Article 42. Stability data supporting the expiration date or retest date of the reference standards must be presented.

CHAPTER V

FINAL AND TRANSITIONAL PROVISIONS

Article 43. Stability studies that compose marketing authorization and post-marketing authorization alteration petitions of biological products submitted before the effectiveness of this Resolution shall be analyzed in accordance with the rules in force at the time of the respective protocols.

Article 44. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, in accordance with Law No. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 45. Collegiate Board Resolution – RDC No. 50 of 20 September 2011, published in the Federal Official Gazette No. 183 of 22 September 2011, page 694, is hereby revoked.

Article 46. This Resolution enters into force on 4 January 2021.

ANTONIO BARRA TORRES

Acting Director-President

ANNEX I

Conditions for the conduction of stability studies of the active substance and intermediate product

TEMPERATURE AND HUMIDITY – LONG-TERM STUDY	TEMPERATURE AND HUMIDITY – ACCELERATED STUDY
25°C ± 2 °C/60% UR ± 5% UR or 30°C ± 2°C/65% UR ± 5% UR or 30°C ± 2°C/75% UR ± 5% UR	40°C ± 2°C 75% UR ± 5% UR
5°C ± 3°C	25°C ± 2°C/60% UR ± 5% UR or 30°C ± 2°C/65% UR ± 5% UR or 30°C ± 2°C/75% UR ± 5% UR
≤-20°C ± 5°C	Temperature and humidity parameters shall be defined by the manufacturer

ANNEX II

Conditions for the conduction of stability studies of the finished product

TEMPERATURE AND HUMIDITY – LONG-TERM STUDY	TEMPERATURE AND HUMIDITY – ACCELERATED STUDY
25°C ± 2 °C/60% UR ± 5% UR (hospital-restricted use products only) or 30°C ± 2°C/65% UR ± 5% UR or 30°C ± 2°C/75% UR ± 5% UR	40°C ± 2°C 75% UR ± 5% UR
5°C ± 3°C	25°C ± 2°C/60% UR ± 5% UR or 30°C ± 2°C/65% UR ± 5% UR or 30°C ± 2°C/75% UR ± 5% UR
≤-20°C ± 5°C	Temperature and humidity parameters shall be defined by the manufacturer

ANNEX III

Conditions for the conduction of stability studies of water-based products

TEMPERATURE AND HUMIDITY – LONG-TERM STUDY	TEMPERATURE AND HUMIDITY – ACCELERATED STUDY
25°C ± 2 °C/40% UR ± 5% UR (hospital-restricted use products only) or 30°C ± 2°C/35% UR ± 5% UR	40°C ± 2°C and not higher than 25% UR