COLLEGIATE BOARD RESOLUTION – RDC NO. 318 OF 6 NOVEMBER 2019

Establishes the criteria for the conduction of Stability Studies for active pharmaceutical ingredients and medicinal products, except biologicals, and gives 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 the Collegiate Board Resolution – RDC no. 255 of 10 December 2018, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 5 November 2019, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and Scope

Article 1. This Resolution establishes the criteria for the conduction of Stability Studies for active pharmaceutical ingredients (APIs), and new, innovative, generic, similar, dynamized, specific, simplified notification, herbal, and radiopharmaceutical medicinal products.

Sole paragraph. This Resolution does not apply to biological products and the active pharmaceutical ingredients used in their manufacture.

Section II

Definitions

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

I – Grouping: Reduced Stability Study model in which only samples of extremes of a given factor are tested at all times. The model assumes that the stability of any intermediate level is represented by the extremes tested;

II – Trend Analysis: part of the statistical analysis that allows to verify the product alteration trend, that is, the variation of certain parameters over time;

III – Storage Conditions: circumstances under which the product should be kept, including conservation care and any other specific recommendations for the storage of APIs and medicinal products;

IV – Conservation Care: recommended temperature and humidity conditions based on the Stability Study for the conservation of APIs or medicinal products;

V – Packaging: wrap, container, or any form of packaging, whether or not removable, intended to cover, package, protect, or maintain, specifically or not, medicinal products and APIs;

VI – Impermeable Packaging: packaging that provides complete barrier to the passage of vapors, gases, or solvents;

VII – Multidose Packaging: packaging from which it is not possible to withdraw a single dosage unit without exposing another dosage unit, which will be used at another time;

VIII – Primary Packaging: packaging that maintains direct contact with the API or medicinal product;

IX – Secondary Packaging: external packaging of the product, which is in contact with the Primary Packaging or Intermediate Wrap, and may contain one or more Primary Packaging;

X – Semipermeable Packaging: packaging that allows the passage of vapors, gases, and solvents;

XI – Intermediate Wrap: packaging that is in contact with the Primary Packaging and that constitutes wrap or any other form of removable protection, and may contain one or more Primary Packaging;

XII – Stability Specifications: set of physical, chemical, and microbiological tests, accompanied by their acceptance criteria, which must be met to ensure adequate quality of the API or medicinal product throughout its Retest Period or Expiry Date;

XIII – Release Specifications: set of physical, chemical, and microbiological tests, accompanied by their acceptance criteria, which must be applied at the time of release of the API or medicinal product by Quality Control, to ensure compliance with the Stability Specifications throughout the product's shelf life;

XIV – Forced Degradation Study: study that allows the generation of degradation products through exposure of the API or finished product to stress conditions, such as light, temperature, heat, humidity, acid/ basic hydrolysis, oxidation, among others;

XV – Stability Study: study designed to test and provide evidence of variation in the quality of the API or medicinal product over time, given the influence of various environmental factors, such as temperature, humidity, and light, in addition to other factors related to the product itself, such as the physical and chemical properties of the API and pharmaceutical excipients, as well as pharmaceutical form, manufacturing process, type, and properties of packaging materials, with the purpose of establishing the API Retesting Period or the Expiry Date for the API and the medicinal product;

XVI – Accelerated Stability Study: study designed to assess possible physical, chemical, and microbiological alterations in APIs or medicinal products, under forced storage conditions, in order to assist in determining the API Retesting Period or the Expiry Date for the API and the medicinal product, as well as to assess the effect of short excursions outside the recommended Conservation Care;

XVII – Follow-up Stability Study: study carried out with the objective of monitoring and confirming the Expiry Date for the API and medicinal product and the API Retest Period;

XVIII – Long Term Stability Study: study designed to verify the physical, chemical, and microbiological characteristics of the API or medicinal product, in the proposed Storage Conditions and Expiry Date, and may also be used to define the API retest period;

XIX – Stability Study in Use: study designed for medicinal products packaged in Multidose Packs, with the purpose of providing initial and final information that confirms the period of use for which the medicinal product maintains its stability, after opening and subsequent reopening of the Primary Package, and storage under the conditions determined by the period of use;

XX – Reduced Stability Study: study designed based on technical-scientific justification, in which part of the samples of each combination of Product Stability Factors is not tested at all times;

XXI – Photostability Study: study that intends to demonstrate that the API or medicinal product, when exposed to light, remains within its specifications;

XXII – Product Stability Factors: product characteristics that influence its stability, which include, but are not limited to: concentration, volume, package shape, and closure system;

XXIII – Impurity: any component present in the API or finished product other than API or excipient(s);

XXIV – Matrixing: statistics-based Reduced Stability Study model, in which one sampling subgroup, selected from the total number of possible samples for all combination factors, is tested in specified time, and another subgroup is tested in the subsequent time. The model assumes that the stability of each sampling subgroup represents the stability of all samples within a given time interval;

XXV – Stability-Indicating Analytical Methods: validated quantitative analytical methods capable of detecting, over time, alterations in the physical, chemical, or microbiological properties of the API or medicinal product, or capable of accurately measuring the content of the active pharmaceutical ingredient, degradation products, and other components of interest without interference;

XXVI – API Retest Period: established period, based on Stability Studies, after which the material must be retested to ensure that it remains suitable for immediate use, according to stability-indicating tests defined by the API manufacturer, maintaining the pre-established Storage Conditions;

XXVII – Shelf Life: time during which the API or medicinal product may be used, characterized as useful life period and based on specific Stability Studies, maintaining the previously established Storage and Transportation Conditions;

XXVIII – Stability Study Protocol: document defining the stability study plan, including tests and acceptance criteria, schedule, characteristics of the batch to be studied, quantity of samples, study conditions, analytical methods, and packaging material;

XXIX – Stability Study Report: document presenting the consolidated results from the Stability Studies.

CHAPTER II

STABILITY STUDIES

Section I

General Provisions

Article 3. The Stability Studies for APIs and medicinal products to be marketed in Brazil shall be conducted whenever specific normative acts providing for marketing authorization or post-authorization alterations require them, and in accordance with the parameters defined in this Resolution.

Sole paragraph. Follow-up Stability Studies shall be conducted as provided in this Resolution, and the respective reports shall be submitted whenever requested by the health authority.

Article 4. In case of imported products and products stored in bulk, additional studies must be conducted to ensure the maintenance of product quality until the Primary Packaging stage.

Article 5. In case of API regularization petitions, marketing authorization of medicinal product with new API in the country, Long-Term Stability Studies in progress should be presented at the moment of submission, , with results of at least 12 (twelve) months, accompanied by completed Accelerated Stability Studies.

Article 6. In case of marketing authorization petitions for medicinal products with API already authorized in the country, for post-authorization of medicinal products, as well as for the marketing authorization of new concentrations and new pharmaceutical forms of APIs already existing in Brazil, and for API post-regularization alterations, Long-term Stability Studies in progress should be presented at the moment of submission, with results of at least 6 (six) months, accompanied by completed Accelerated Stability Studies.

Sole paragraph. The provisions in the caption of this article do not apply to post-authorization alterations to medicinal products for which specific normative acts in force allow the presentation of the Accelerated and Long-Term Stability Study Protocol for the petition submission.

Article 7. The completed Accelerated Stability Study shall be submitted even if the Long Term Stability Study is completed.

Sole paragraph. The provisions in the caption of this article do not apply to post-authorization alterations to medicinal products for which specific normative acts in force allow the presentation of the Accelerated and Long Term Stability Study Protocol for the submission of the petition.

Article 8. Stability protocols and reports and raw data must be made available whenever requested by the competent health authority.

Article 9. If there is an out-of-specification result in a Stability Study, the medicinal product marketing authorization holder is responsible for the conduction of the necessary investigations to identify the root cause of the results.

Paragraph 1. If the investigation referred to in the caption of this article is inconclusive or concludes that the result was not due to an analytical error, the responsible company must notify Anvisa, also informing the measures taken to mitigate the health risk.

Paragraph 2. The notification referred to in Paragraph 1 is not necessary when the study refers to a product with marketing authorization not yet filed, or condition regarding post-authorization alteration not yet filed.

Article 10. Grouping and Matrixing models may be accepted as a Reduced Stability Study.

Sole paragraph. The use of reduced model will only be accepted if the data obtained are representative of the tested and untested points.

Article 11. The Stability Study data in reduced model should be assessed according to the same models and techniques used for the data of a complete study model.

Sole paragraph. Failure of a test at any given time implies in failure of all other samples represented by the reduced study.

Article 12. When any of the requirements in this Resolution is not applicable, its non-compliance must be accompanied by technical justification and data supporting its absence.

Section II

Accelerated, Long-Term, and Follow-Up Stability Study for APIs and medicinal products

Article 13. API Long-Term and Follow-up Stability Studies shall be conducted in accordance with Annex I of this Resolution.

Article 14. Accelerated, Long-Term, and Follow-up Stability Studies for medicinal products shall be conducted under the temperature and humidity conditions provided for in Annex II of this Resolution.

Paragraph 1. When the packaging used in the Stability Study is proven to be impermeable to humidity, it shall not be necessary to conduct the study under the humidity conditions provided for in Annex II of this Resolution.

Paragraph 2. In the case of water-based products in semipermeable packaging, the study shall be allowed to be carried out in conditions of humidity other than those provided for in Annex II, provided that the weight loss result is corrected to the reference humidity through a scientifically valid calculation.

Article 15. It is allowed to conduct Long-Term Stability Study and follow-up in a condition different from that provided for in Article 14 when the medicinal product is used exclusively in specialized hospitals and clinics, and the impossibility of adopting the conditions set out in Annex II of this Resolution is demonstrated, in which case the study for the medicinal product should be conducted at 25°C ± 2°C/60% RH ± 5% RH.

Article 16. APIs and medicinal products that require Storage Conditions other than those provided for in this Resolution shall be treated on a case-by-case basis, considering that the stability studies presented must ensure feasible shelf lives and storage precautions for the product.

Article 17. If the API or medicinal product with a storage condition of 2°C to 8°C presents out-of-specification results in the first 3 (three) months of the Accelerated Stability Study, the effect of short-term variations outside the recommended Storage Conditions shall be assessed, subject to the conditions described for shipping or handling.

Paragraph 1. In the cases provided for in the caption of this article, the Expiry Date for medicinal products or APIs, or the API Retest Period shall be based only on Long-Term Stability Studies.

Paragraph 2. The assessment referred to in the caption of this article shall be based on additional studies conducted in 1 (one) batch of the API or medicinal product, for a period shorter than 3 (three) months, through the conduction of tests more frequently.

Paragraph 3. In the cases provided for in the caption of this article, it is not necessary to continue the study for up to 6 (six) months.

Article 18. Accelerated Stability Studies are not necessary for API or medicinal product with storage condition from -25°C to -15°C.

Paragraph 1. In the cases provided for in the caption of this article, the Expiry Date for medicinal products or APIs and the API Retest Period shall be based only on Long-Term Stability Studies.

Paragraph 2. In the cases provided for in the caption of this article, additional studies shall be required to determine the effect of short intervals of material permanence outside the Storage Conditions described on the label, in accordance with the conditions described for handling, shipping, and transportation.

Article 19. The Follow-up Stability Study shall be carried out as provided for in the Resolution on Good Manufacturing Practices.

Section III

Post-reconstitution or Dilution Stability Study for medicinal products

Article 20. For medicinal products requiring reconstitution or dilution before use, an additional study should be conducted to determine the Shelf Life in use of the finished product.

Article 21. The Post-reconstitution or dilution Stability Study shall be conducted under one of the Long-Term Stability Study conditions defined in Annex II of this Resolution, presenting:

I – initial result, which corresponds to the product immediately after reconstitution or dilution; and

II – final result, which corresponds to the reconstituted and diluted product for the maximum period recommended.

Article 22. The medicinal product shall be waived from the Stability Study after reconstitution or dilution when the following two conditions are met:

I – administration immediately after reconstitution or dilution is explicitly recommended in the package leaflet; and

II – the Primary Packaging is not Multidose.

Article 23. The Stability Study after reconstitution or dilution must be conducted in at least 2 (two) batches of Long-Term Stability Studies submitted at the moment of marketing authorization and in 1 (one) batch in post-authorization alterations.

Paragraph 1. If the post-authorization alteration does not have a potential impact on the reconstitution or dilution of the product, the study may be waived upon technical justification.

Paragraph 2. If there is evidence of instability after reconstitution or dilution, this study may be requested in all batches for which the Long-Term Stability Study is presented, as well as in the Follow-up Stability Studies.

Article 24. Stability after reconstitution or dilution shall be tested at least at the initial and end times of the Long-Term Stability Study.

Sole paragraph. When there is a submission with a Stability Study in progress, stability after reconstitution or dilution shall also be tested within 12 months or in the latest period available before petition.

Article 25. The Stability Study after reconstitution or dilution must be conducted using all the diluents for reconstitution or dilution specified in the package insert.

Article 26. In the Stability Study after reconstitution or dilution, in addition to the provisions in Article 21, a study must be presented to prove the stability of the medicinal product against exposure to light under the conditions of use.

Article 27. In the Stability Study after reconstitution or dilution, all tests provided for in the protocol of the Long-Term Stability Study shall be conducted for the periods provided for in items I and II of Article 21 of this Resolution.

Sole paragraph. When any test is not conducted or the specifications are altered, the corresponding technical justification must be presented.

Section IV

In-Use Stability Study for medicinal products

Article 28. For medicinal products packaged in Multidose Packs, an additional study should be conducted to determine the Shelf Life of the product after opening.

Article 29. The in-use stability study shall be conducted under one of the conditions of the Long-Term Stability Study defined in Annex II of this Resolution, and shall simulate the use of the product.

Article 30. The In-Use Stability Study must prove stability, at least, for the estimated period for the permanence of the medicinal product in its Primary Packaging, after opening, presenting:

I – initial result, which corresponds to the product before or immediately after opening; and

II – result at the end of the period of use.

Article 31. The In-Use Stability Study must be conducted in at least 2 (two) batches of the Long-Term Stability Studies submitted at the moment of marketing authorization, and in 1 (one) batch in post-authorization alterations, and at least one batch must be assessed at the end of its shelf life.

Paragraph 1. If the post-authorization alteration does not have a potential impact on in-use stability, the study may be waived upon technical justification.

Paragraph 2. If there are indications of in-use instability, the in-use stability study may be requested in the other Stability Studies referred to in this Resolution.

Article 32. In-use stability should be tested at least at the initial and end times of the Long-Term Stability Study.

Sole paragraph. When there is submission with a Stability Study in progress, in-use stability shall also be tested within 12 months or in the latest period available before petition.

Article 33. For medicinal products with defined dosage, the In-Use Stability Study must prove stability for the maximum duration of treatment, considering the lowest dosage.

Article 34. For medicinal products with no defined minimum dosage or of occasional use, the In-Use Stability Study should be conducted in accordance with one of the following three options:

I – until the Expiration Date proposed for the closed product;

II – until there is failure in any test; or

III – until the pre-established validity period after opening, considering previous results from the In-Use Stability Study.

Article 35. In the In-Use Stability Study, all tests provided for in the protocol of the Long-Term Stability Study shall be performed for the times provided for in items I and II of Article 30 of this Resolution.

Sole paragraph. When any test is not conducted or the specifications are altered, the corresponding technical justification must be presented.

Section V

Forced Degradation Study

Subsection I

Forced Degradation Study in APIs

Article 36. Forced Degradation Study in APIs must be conducted in 1 (one) batch.

Article 37. The effects of temperature, humidity, oxidation, light, and susceptibility to hydrolysis over a wide range of pH values should be included in the Forced Degradation Study in APIs.

Sole paragraph. Failure to conduct the study under any of the conditions mentioned in the caption of this article must be technically justified.

Article 38. For the purpose of development and validation of the analytical methodology, Forced Degradation Studies shall promote degradation to an extent sufficient to assess the formation of degradation products, and less than that which would lead to excessive and complete degradation of the API sample.

Paragraph 1. The studies referred to in the caption of this article may be finalized after an evident level of decomposition, which exceeds the analytical variations of the method.

Paragraph 2. The exposure levels used by the company and the absence of degradation shall be justified.

Article 39. When there is proof that certain impurity(ies) is (are) not formed under Accelerated and Long-Term Stability conditions, it will not be necessary to test them in Accelerated, Long-Term, and Follow-Up Stability Studies.

Subsection II

Forced Degradation Study in Medicinal Products

Article 40. For new, generic, and similar medicinal products, Forced Degradation Studies shall be conducted in accordance with the rule providing for notification, identification, and qualification of degradation products in medicinal products.

Article 41. For herbal, specific, dynamized, simplified notification medicinal products, and radiopharmaceuticals, the degradation products quantification in Stability Studies should be performed when:

I – degradation products are mentioned in official compendium monographs; or

II – regarding degradation products that present relevant toxicity or that may generate therapeutic ineffectiveness.

Article 42. Forced Degradation Studies should also be used to identify if there is any condition to which the API or medicinal product is particularly sensitive.

CHAPTER III

PROCEDURE FOR STABILITY AND PHOTOSTABILITY STUDIES

Section I

Conducting the Stability Study

Article 43. For Stability Studies, the sampling procedures adopted shall ensure full representativeness and homogeneity of the batch(es) studied.

Article 44. The impact of packaging composition and its closure system on product stability must be assessed throughout the Shelf Life.

Article 45. Stability studies must be conducted with the medicinal product in the packaging proposed for commercialization, including, as appropriate, the secondary packaging or the intermediate wrap.

Article 46. Samples intended for the API Stability Study must be placed in containers with the same chemical composition and physical characteristics as the commercial packaging.

Sole paragraph. API stability studies shall be accepted with the APIs packed in packages smaller than commercial size, as long as they maintain the other physical and chemical characteristics.

Article 47. Stability-Indicating Analytical Methods should be used in stability analyzes.

Article 48. Substitution or alteration of analysis methods during the stability study is only allowed when:

I – the methods are equivalent or the proposed method is superior to the one used; and

II – there is no impact on trend result analysis, when applicable.

Paragraph 1. Substitution or alteration of analysis methods must be technically justified.

Paragraph 2. If there is a proposal for a new method that does not fit the caption of this article, it may only be added to the study, without excluding or altering the previous method.

Article 49. The methods used in stability studies must be validated in accordance with the normative act that provides for the validation of analytical methods.

Section II

Stability Study Assessment

Article 50. The results obtained in the study must be assessed to verify which attributes are subject to alteration over time and that may impact the quality of the API and the medicinal product, as well as the performance of the medicinal product.

Article 51. Statistical assessment of Long-Term Stability Studies should be performed when necessary, in order to indicate provisional shelf life and to ensure that the proposed Shelf Life or Retest Period is applicable for all batches manufactured under similar conditions.

Sole paragraph. Formal statistical assessment is not necessary when there is no significant variation in the results assessed.

Article 52. Statistical evaluation of Long-Term Stability Study test results shall include inter-batch variation and Trend Analysis where applicable.

Sole paragraph. The statistical assessment must assess, on a separate basis, quantitative content results, degradation products, and any other appropriate attributes.

Article 53. The influence of inter-batch variation on the outcome of the Trend Analysis must be assessed.

Article 54. Out-of-trend results must be investigated and justified.

Article 55. The non-use of a statistical method for trend assessment and for inter-batch variation in the long-term stability study must be justified.

Article 56. The Release and Stability Specifications shall be defined during the development of the API or medicinal product, so that it minimally complies with the requirements applicable to the medicinal product or API in question during its entire Shelf Life or Retest Period.

Section III

Conducting the Photostability Study

Article 57. Photostability studies must show the effects of exposure to light on the quality of the API or medicinal product.

Article 58. The temperature inside the photostability chamber must be adequately controlled.

Article 59. The photostability camera must be optically isolated.

Article 60. The light source must be accompanied by the manufacturer's spectral specification and be in accordance with the protocol defined by the company.

Article 61. A light source with a spectral composition of recognized pattern, including the wavelengths of ultraviolet and visible regions, must be used.

Article 62. The samples must be exposed to at least 1.2 million lux hours and an ultraviolet energy of at least 200 watt hours/ m^2 in a duly qualified system.

Article 63. In order to ensure compliance with the provisions of Article 62 of this Resolution, exposure of the samples to the light source must occur in conjunction with the qualified chemical actinometric system or qualified radiometers/ luxmeters.

Article 64. Qualification data of the light source and the actinometric system used must be made available whenever requested by the health authority.

Article 65. The samples must be arranged in such a way that all their units or all their contents are directly exposed to light.

Article 66. All directly exposed samples must be placed in containers of chemically inert material.

Article 67. If protected samples are used as controls to assess the alterations caused by the temperature induced in the process, they must be packed together with the samples under test.

CHAPTER IV

SPECIFIC REQUIREMENTS FOR THE CONDUCTION OF API STABILITY STUDIES

Section I

Tests

Article 68. In the API Stability Study, all quality attributes that have a potential impact on quality, efficacy, and safety, and which may be altered under the influence of time, temperature, humidity, or any other exposure factor, must be tested.

Section II

Stability Study Protocol and Report

Article 69. The API Stability Study Protocol must contain the following information:

I – API identification according to the Brazilian Common Denomination (DCB), International Nonproprietary Name (INN), or Chemical Abstract Service (CAS);

II – tests to be conducted, informing the acceptance criteria;

III – execution schedule;

IV – name and address of the API manufacturer;

V – conditions of the study;

VI – Stability-Indicating Analytical Methods used in all tests; and

VII – packaging material used.

Article 70. The API Stability Study Report must present, in tabular form, the results obtained from the assessment conducted in accordance with the provisions of the protocol.

Article 71. The API Stability Study Report, in addition to the information contained in the protocol, must include:

I – batch number(s);

II – batch size(s);

III – packaging material description;

IV – batch manufacturing date(s);

V – study initial date (day/ month/ year);

VI – storage conditions;

VII – frequency of the tests;

VIII – Stability Specifications;

IX – results of the tests conducted;

X – statistical assessment of results, if applicable; and

XI – Conclusion.

Sole paragraph. Where any of the information described in the items of this article is not included in the study report, the corresponding technical justification must be presented.

Article 72. The conclusion of the Stability Study Report must:

I – address how the API quality varies over time

II – establish the Expiration Date or Retest Period; and

III – recommend the Storage Conditions.

Sole paragraph. At the conclusion of the Stability Study Report, the company must inform explicitly if an Expiration Date or Retest Period is being defined.

Article 73. The study protocol and report shall be required for Accelerated and Long-Term Stability Studies, Photostability Studies, and Forced Degradation Studies.

Paragraph 1. If the Forced Degradation Study, pursuant to this Resolution, has been carried out in the validations of analytical methodologies, there is no need to present a new Forced Degradation Study in the stability section.

Paragraph 2 Presentation of the protocol is optional when the study report is complete and includes the information required in the protocol.

Section III

Batch Selection

Article 74. Accelerated and Long-Term Stability Studies must be conducted with at least 3 (three) batches of API.

Paragraph 1. The batches must be at least manufactured in pilot scale, through the same synthesis route, and with a manufacturing procedure method that simulates the final process that will be applied in industrial batches.

Paragraph 2. The overall quality of the API batches must be representative of the quality of the batches to be manufactured on an industrial scale.

Paragraph 3. The required quantity of batches may be less than 3 (three), due to regulation in a ruling that provides for the regularization of APIs.

Article 75. Follow-up Stability Studies must be conducted with at least one (1) API batch per year, unless no API batch has been produced in the year.

Section IV

Expiry Date and Retest Period

Article 76. The API Expiry Date or Retest Period must be determined by a Long-Term Stability Study, in accordance with the parameters defined in this Resolution.

Article 77. The batches to be sampled must be representative of the manufacturing process.

Article 78. The Provisional Expiration Date or Provisional Retest Period shall be established from the statistical analysis of the results presented, limited to the addition of 12 months, considering the Accelerated Stability Study completed and the Long-Term Stability Study in progress.

Sole paragraph. If the statistical analysis is not applicable, the technical and rational justification to define the Expiration Date or Retest Period must be presented.

Section V

Frequency of API Stability Tests

Article 79. For Accelerated Stability Studies, the following tests must be conducted, when provided for in the protocol, at the initial time, in the 3rd and 6th months of the study:

I – aspect;

II – API content;

III – quantification of individual and total degradation products; and

IV – identification of degradation products, when applicable.

Article 80. For Long-Term Stability Studies, the same tests provided for in Article 79, at least, must be performed at the initial time, every 3 (three) months during the first year, every 6 (six) months during the second year, and annually, after the 24th month, until the end of the Validity Period or Retest Period.

Sole paragraph. The other tests must be conducted at the end of the Accelerated, Long-Term, and Follow-up Stability Studies, considering the initial time as reference.

Article 81. In the case of submissions for marketing authorization or post-authorization alterations with studies in progress, all tests provided for in the protocol must be performed at least prior to the petition.

Section VI

Photostability Study

Article 82. The Photostability Study must be conducted with 1 (one) representative batch of the API production.

Sole paragraph. In case of inconclusive results, the study should be repeated with 2 (two) additional representative batches of the API production.

Article 83. The Photostability Study must be conducted with the API outside its commercial packaging, completely exposed to the light source.

Paragraph 1. The use of inert transparent packaging is allowed, when justified.

Paragraph 2. If there is an out-of-specification result, that is, in case the API photosensitivity is presumed with scientific bibliography showing such behavior, the study must be conducted with the API inside the photoprotective packaging, observing the packaging specifications to be adopted for the commercialized API.

Article 84. After exposure to the light source, according to Article 83 of this Resolution, all tests necessary to ensure the maintenance of API quality must be conducted.

Article 85. Based on the results from Photostability Studies, the company must:

I – inform the precautions to be taken during the manufacture or formulation of medicinal products that use the API; and

II – inform about the need to use light-resistant packaging for the API.

CHAPTER V

SPECIFIC REQUIREMENTS FOR THE CONDUCTION OF STABILITY STUDIES IN MEDICINAL PRODUCTS

Section I

Tests

Article 86. In the Stability Study of the medicinal product, all quality attributes that have a potential impact on quality, efficacy, and safety, and which may be altered under the influence of time, temperature, humidity, or any other exposure factor, must be tested.

Section II

Stability Study Protocol and Report

Article 87. The Stability Study Protocol must contain the following information:

I – name of the medicinal product and API identification according to the Brazilian Common Denomination (DCB), International Nonproprietary Name (INN), or Chemical Abstract Service (CAS);

II – tests to be conducted and Stability Specifications;

III – execution schedule;

IV – the following characteristics of the batch under study:

a) name and address of the manufacturer of the medicinal product;

b) manufacturing process, when there is more than one; and

c) batch size.

V – conditions of the study;

VI – Stability-Indicating Analytical Methods used in all tests; and

VII – primary packaging material

Article 88. The Stability Study Report must present, in tabular form, the results obtained from the assessment conducted in accordance with the provisions in the protocol.

Article 89. The Stability Study Report, in addition to the information contained in the protocol, must include:

I – batch manufacturing date;

II – presentation;

III – batch of the API used;

IV – manufacturing date of the API used;

V – name and address of the manufacturer of the API used;

VI – bulk product batch, when applicable;

VII – intermediate product batch, when applicable;

VIII – number and size of the finished product batch;

IX – study initial date (day/ month/ year);

X – frequency of tests;

XI – production process, in case there is more than one approved production process;

XII – test results;

XIII – statistical assessment of results, if applicable; and

XIV – conclusion.

Article 90. The conclusion must:

I – address how the quality of the medicinal product varies over time, due to the influence of the conditions of the studies conducted;

II – suggest the product's Expiration Date; and

III – recommend the conditions of its storage.

Article 91. The study protocol and report shall be required for Accelerated and Long-Term Stability Studies, Photostability Studies, Post-Reconstitution and Dilution Stability Studies, as well as In-Use Stability Studies, where such studies are required.

Sole paragraph. The presentation of the protocol is optional when the study report is complete and includes the information required in the protocol.

Section III

Batch Selection

Article 92. The batches of the medicinal product used in the Stability Studies must meet the following criteria:

I – have the same formula and the same primary packaging as those claimed in the petition; and

II – comply with the requirements to be classified as a pilot batch or be an industrial batch.

Paragraph 1. When Stability Studies of 3 (three) batches are presented, it will be allowed, as long as technically justified, that 1 (one) of these batches is smaller than the pilot scale, provided that it is representative of the critical stages of the production process and formulation.

Paragraph 2. When Stability Studies are presented in accordance with the provisions of the caption of this article, but smaller than the proposed industrial size, they must be accompanied by a Stability Study protocol of the corresponding quantity of industrial size batches.

Article 93. The number of batches to be selected for the conduction of Accelerated and Long-Term Stability Studies must follow the current specific normative act that provides for marketing authorization or post-authorization alterations, accordingly.

Sole paragraph. In cases where the proposed condition in the marketing authorization or post-authorization alterations is different from the condition of the batches in the stability study, a technical justification with scientific rationale must be presented that allows the stability data to be extrapolated to the proposed condition.

Section IV

Expiry Date

Article 94. The Validity Period shall be determined by Accelerated and Long-Term Stability Studies, carried out in accordance with the parameters defined in this Resolution.

Paragraph 1. The period referred to in the caption of this article shall be definitively fixed only after assessment of the Long-Term Stability Study completed.

Paragraph 2 If there is presentation of results from completed Accelerated Stability Study and Long-Term Study in progress, the provisional Expiry Date shall be established from the statistical analysis of the results presented and relevant historical data, limited to the addition of 12 months.

Paragraph 3. If the statistical assessment is not necessary, a justification must be presented.

Paragraph 4. When significant alterations occur during the period of 3 (three) to 6 (six) months of the Accelerated Stability Study, the provisional Expiry Date shall be based on the statistical assessment of available data from the Long-Term Stability Study.

Paragraph 5. The following are considered significant alterations:

I – 5% loss in content in relation to the initial value or out-of-specification result for potency through a microbiological or immunological method, except for medicinal products containing herbal and opotherapeutic APIs;

II – any result outside the specified limit;

III – dissolution with result outside the specified limit for 12 (twelve) units;

IV – significant alterations in the chromatographic profile or 10% loss in API content for medicinal products containing herbal and opotherapeutic APIs; or

V – weight loss greater than or equal to 5% in 3 months.

Paragraph 6. For packages that are not multidose or bottles smaller than 1mL, weight loss greater than or equal to that described in item V of paragraph 4 of this article shall be technically justified.

Paragraph 7. Depending on the pharmaceutical form, there may be technical justification for the alterations not to be considered significant.

Section V

Frequency of Stability Tests

Article 95. For the Accelerated Stability Study, the following tests shall be conducted, when provided for in the protocol, at the initial time, in the 3rd and 6th months of the study:

I – aspect

II – content;

III – quantification of degradation products;

IV – dissolution or performance testing of the product, depending on the pharmaceutical form;

V – pH; and

VI – quantification of antimicrobials and antioxidants.

Paragraph 1. For medicinal products containing herbal and opotherapeutic APIs, in addition to the tests provided for in the caption of this article, a disintegration test must be conducted at all times.

Paragraph 2. For dynamized medicinal products, in addition to the tests provided for in the caption of this article, a disintegration and humidity test must be conducted at all times, if applicable to the pharmaceutical form.

Article 96. For the Long-Term Stability Study, the same tests listed in Article 95 must be conducted:

I – at the initial time;

II – every 3 (three) months during the first year;

III – every 6 (six) months during the second year; and

IV – annually from the third year of the proposed Validity Period.

Article 97. Other tests considered important for trend analysis must also be performed at the times provided for in articles 94 and 95 of this Resolution.

Sole paragraph. The other tests should be performed minimally at the start and end times.

Article 98. In the case of submissions of marketing authorization or post-authorization alterations with studies in progress, all tests provided for in the protocol must be performed at least prior to submission.

Section VI

Photostability Study

Article 99. The Photostability Study must be conducted on the medicinal product outside its Primary Packaging, completely exposed to the light source.

Paragraph 1. The use of protective inert transparent packaging is allowed, when justified.

Paragraph 2. The medicinal product shall be considered photostable if there are no results out of specification.

Paragraph 3. If the study provided for in the caption of this article is not carried out, a technical justification must be presented and the study provided for in Article 100 must be conducted.

Article 100. If there is result outside the specification in the study referred to in Article 99, the study must be conducted on the medicinal product within the proposed Primary Packaging, subject to the same Primary Packaging specifications to be used on the commercialized product.

Sole paragraph. If no result is out of specification, the medicinal product shall be considered photostable, as long as it is kept in its Primary Packaging.

Article 101. Only if it is not possible to obtain results within the specifications of the test referred to in Article 100 of this Resolution, and when it is technically proven impossible to use Primary Packaging with a higher degree of photoprotection, a new Photostability Study of the product may be conducted on its Primary Packaging added with another protection, which may be the Secondary Packaging or an Intermediate Wrap.

Paragraph 1. If there is no result out of specification, the medicinal product shall be considered photostable, as long as it is kept in its Secondary Packaging.

Paragraph 2. If the additional protection is the Secondary Packaging, only presentations with 1 (one) unit per Secondary Packaging shall be allowed.

Article 102. For the purposes of marketing authorization or inclusion of new concentrations or pharmaceutical forms, the Photostability Study must be conducted initially on 1 (one) batch that has the same formula and simulates the production process intended to be authorized.

Paragraph 1. The study must be repeated in more than 1 (one) batch that meets the requirements for pilot batch or industrial batch.

Paragraph 2. If the batch mentioned in the caption of this article already meets the requirements of Paragraph 1 of this article, it is not necessary to repeat the study.

Paragraph 3. If the results of the study described in the caption of this article are not conclusive, a study must be conducted in 2 (two) additional batches.

Article 103. For post-authorization alterations where the Photostability Study is not waived, it may be conducted in only 1 (one) batch.

Article 104 . At the end of the light exposure period, the samples must be analyzed for any alterations in physical characteristics and chemical properties.

CHAPTER VI

DYNAMIZED MEDICINAL PRODUCTS

Article 105. In the case of compared pharmaceutical forms, data from a Stability Study conducted in a dynamized medicinal product may be used as a reference for the definition of the Shelf Life of another dynamized medicinal product.

Paragraph 1. Compared pharmaceutical forms are considered as the dynamized medicinal products of the same company that have the same pharmaceutical form, the same excipients, the same manufacturing location, the same manufacturing process, and the same Primary Packaging specifications, provided that they do not have any API in dilution less than 1 (one) part to 10,000 (ten thousand) vehicle parts in the finished product.

Paragraph 2. In the case of compared dosage forms, the Stability Studies must be conducted with the dynamized medicinal product that contains the less dynamized API.

CHAPTER VII

LABELING

Article 106 . The API Shelf Life or Retest Period and the Shelf Life of the medicinal product, determined based on Stability and Photostability Studies conducted as described in this Resolution, must be informed on their respective labels.

Article 107. All Storage Conditions recommendations based on the Stability and Photostability Studies must be stated on the API label, labeling, and package insert, or equivalent document in accordance with specific regulation in force, and specific instructions must be provided, where applicable.

Paragraph 1. When the medicinal product fails the photostability study when completely exposed to the light source, the warning stating it must be protected from light must be added to its labeling.

Paragraph 2. When the medicinal product fails the photostability study conducted within the proposed primary packaging, a specific warning must be added to its label and package insert, stating the medicinal product must be promptly returned to the Secondary Packaging or Intermediate Wrap after administration.

Paragraph 3. When the medicinal product is used exclusively in hospitals and specialized clinics, and stability is proven only at 25°C ± 2°C/60% RH ± 5% RH, a specific warning must be added to its label and package insert, stating the medicinal product must be stored below 25°C.

Paragraph 4. The phrases corresponding to Conservation Care and Shelf Life after reconstitution or dilution must be included in the package insert and labeling of medicinal products requiring reconstitution and dilution.

Paragraph 5. The phrases corresponding to the Conservation Care and Shelf Life of the product after opening must be included in the package insert and labeling of medicinal products packaged in Multi-dose Packaging.

Paragraph 6. If other specific sensitivity of the medicinal product is detected, it must be indicated on the label and package insert.

CHAPTER VIII

FINAL AND TRANSITIONAL PROVISIONS

Article 108. For simplified notifications of medicinal products, studies that are in accordance with the regulations provided for in Article 114 of this Resolution shall be accepted if all the following conditions are met:

I – the study was finalized before the publication of this Resolution, while the respective notification to Anvisa will be made in up to 6 (six) months from the publication of this Resolution; or

II – the study was initiated before the publication of this Resolution, while the respective notification to Anvisa will be made in up to 24 (twenty-four) months from the beginning of the study.

Article 109. The Follow-up Stability Study must be conducted in accordance with the protocol approved in the last petition mentioned in Article 111 of this Resolution.

Article 110. For simplified notification medicinal products, which were notified before the publication of this Resolution, Follow-up Stability Studies shall be accepted according to the Resolutions mentioned in Article 114, provided that these studies are completed in up to 36 (thirty-six) months after the date this Resolution is published.

Article 111. For medicinal product marketing authorization and post-authorization alteration petitions, and regularization or API alteration petitions, when Stability Studies are requested, studies that comply with the regulations referred to in Article 114 of this Resolution shall be accepted, provided that one of the following conditions is met:

I – in any case, the study must have been completed prior to the publication of this Resolution, while the respective petition must have been submitted in up to 6 (six) months from the date this Resolution is published;

II – in the case of post-authorization alterations to medicinal products, or post-regularization alterations to the API, the study must have been initiated prior to the publication of this Resolution, while the respective petition must have been submitted in up to 6 (six) months from the expiry date of the oldest batch of this study, considering the Expiry Date approved at the time of the protocol; or

III – in the case of marketing authorization of medicinal products or API regularization, the study must have been initiated prior to the publication of this Resolution, while the respective petition must have been submitted in up to 24 (twenty-four) months from the beginning of the study.

Article 112. Failure to comply with the provisions of this Resolution constitutes a health infraction, pursuant to Law No. 6,437/1977, without prejudice to the applicable civil, administrative and criminal liability.

Article 113. Item 1 of the Annex to Normative Instruction no. 2 of 30 March 2009, published on the Federal Official Gazette of 1 April 2009, is now effective with the following wording:

"1. Primary Considerations

....

For the production of pilot batches it is permissible to have a pilot plant containing equipment with reduced capacity and the same operating principle as that used in the production of the industrial batch.

Pilot batches must be manufactured in accordance with the Good Manufacturing Practices." (new wording)

Article 114 . The following are hereby revoked:

I – Resolution – RE no. 1 of 29 July 2005;

II – Resolution – RDC No. 45 of 9 August 2012;

III – item 5.6.3 of Resolution – RDC No. 08 of 2 January 2001;

IV – Normative Instruction – IN No. 4 of 11 April 2007;

V – Service Guideline No. 02/2013-GGMED/ANVISA of 1 February 2013; and

VI – Service Guideline No. 01/2012-GGMED/ANVISA of 17 October 2012.

Article 115 . This Resolution comes into force on the date of its publication.

WILLIAM DIB

Director-President

ANNEX I

STORAGE CONDITIONS AND CONDITIONS FOR THE CONDUCTION OF LONG-TERM, FOLLOW-UP, AND ACCELERATED STABILITY STUDY OF API

Storage Condition	Long-Term or Follow-up Study *	Accelerated Stability Study *
-25°C to -15°C	-20°C ± 5°C	None
Refrigeration (2-8°C)	5 ± 3°C	25°C ± 2°C/60% RH ± 5% RH or 30 C ± 2°C/75% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH
Controlled ambient temperature (between 15°C and 25°C)	25°C ± 2°C/60% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
Ambient temperature (between 15°C and 30°C) – protect from moisture	30°C ± 2°C/70% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
	30°C ± 2°C/65% RH ± 5% RH	
Ambient temperature (between 15°C and 30°C)	30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH

* The temperatures and relative humidity values for the studies are exactly as described in this table. The variations described are expected and tolerated due to climate chamber openings.

ANNEX II

STORAGE CONDITIONS AND CONDITIONS FOR THE CONDUCTION OF LONG-TERM AND FOLLOW-UP STABILITY STUDY OF MEDICINAL PRODUCTS

Storage Condition	Long-Term or Follow-up Study *	Accelerated Stability Study *
-25°C to -15°C	-20°C ± 5°C	None
Refrigeration (2-8°C)	5 ± 3°C	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH
Ambient temperature (between 15°C and 30°C) – water-based products	30°C ± 2°C/35% RH ± 5% RH	40°C ± 2°C/25% RH ± 5% RH
Ambient temperature (between 15°C and 30°C) – other products	30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH

* The temperatures and relative humidity values for the studies are exactly as described in this table. The variations described are expected and tolerated due to climate chamber openings.