COLLEGIATE BOARD RESOLUTION – RDC NO. 45 OF 9 AUGUST 2012

Provides on the conduction of stability studies on active pharmaceutical ingredients.

The Collegiate Board of Directors of the Brazilian Health Surveillance Agency, in the use of the attributions vested in it under Article 15, items III and IV of Law no. 9,782, dated 26 January 1999, item II, and Paragraphs 1 and 3 of Article 54 of the Internal Regulation approved by Annex I of Anvisa Decree no. 354 dated 11 August 2006, republished on the D.O.U. of 21 August 2006, and its updates, considering the provisions of items III of Article 2, III and IV of Article 7 of Law no. 9,782 of 1999, and the Program to Improve the Agency's Regulation Process, created by Anvisa Decree no. 422, dated 16 April 2008, in a meeting held on 27 July 2012, adopts the following Collegiate Board Resolution and I, Director-President, determine its publication:

Article 1. The Technical Regulation that establishes the minimum requirements for the conduction of stability studies on active pharmaceutical ingredients is approved, in the terms of this Resolution.

CHAPTER I
INITIAL PROVISIONS

Article 1. This Resolution approves the Technical Regulation for the conduction of stability studies on active pharmaceutical ingredients in order to predict, determine, or follow up their retest date or their validity date.

Section I
Scope

Article 2. The manufacturers of active pharmaceutical ingredients must follow the directives established in this Resolution.

Section II
Definitions

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

I – Retest date – Date established by the active pharmaceutical ingredient manufacturer, based on stability studies, after which the material must be retested to ensure it is still adequate for immediate use, in accordance with stability tests defined by the active pharmaceutical ingredient manufacturer, keeping the pre-established storage conditions.

II – Package – Casing, recipient, or any form of wrapping, either removable or not, designed to cover, package, pack, protect, or keep, specifically or not, active pharmaceutical ingredients.

III – Primary package – Casing in direct contact with the active pharmaceutical ingredient, which may be a recipient, wrapping, or any other form of protection, either removable or not, designed to pack or keep, cover or package active pharmaceutical ingredients.

IV – Accelerated stability study – Study designed to accelerate possible chemical degradation and/ or physical alterations of active pharmaceutical ingredients in forced storage conditions. The data obtained from such process, together with those from long term studies, may be used to assess prolonged chemical and physical effects in non-accelerated conditions, as well as to assess the impact of short exposures in conditions other than those established on the active pharmaceutical ingredient label.

V – Long term stability study – Study designed to verify physical, chemical, biological, and microbiological characteristics of an active pharmaceutical ingredient and, as an option, after the retest date or the expected validity date. The results are used to establish or confirm the retest date or validity date and recommend storage conditions.

VI – Impurity – Any undesired component present in the intermediary product or in the active pharmaceutical ingredient.

VII – Active Pharmaceutical Ingredient – API – Any substance introduced in the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient, and may have a pharmacological activity or other direct effect on the diagnosis, cure, treatment, or prevention of a disease, and it also may affect the human body's structure and operation.

VIII – Intermediate product – Substance that suffers molecular alteration or purification, obtained during the processing phases before becoming an active pharmaceutical ingredient.

IX – Batch – A specific quantity of active pharmaceutical ingredient obtained from a process or series of processes, in order to be homogeneous, within the limits established. In the case of continuous production, a batch may correspond to a defined fraction of production. The batch size may also be defined by a fixed quantity or by a quantity produced in a fixed period of time.

X – Pilot-scale batch – A batch of active pharmaceutical ingredient produced through a process equivalent to the one applied to industrial production batches.

XI – Validity period – Period of time during which the active pharmaceutical ingredient may be used, characterized as shelf life, based on specific stability studies, and maintaining the storage and transportation conditions established.

XII – Degradation/ Decomposition product – A molecule resulting from a chemical alteration occurred in the intermediate product or active pharmaceutical ingredient due to the action of time and/ or the action of external agents, such as light, temperature, pH, water, or through the reaction to an excipient and/ or to the primary package.

XIII – Label – Printed, lithographed, painted, fire-engraved, pressure-engraved, or self-adhesive identification applied directly on recipients, packages, casings, or any external or internal package protector, which cannot be removed or altered during the active pharmaceutical ingredient use or during its transportation or storage.

XIV – Forced degradation tests – Tests carried out to assess the intrinsic stability of the active pharmaceutical ingredient as part of the development strategy, executed under harder conditions than the ones used in the accelerated stability study.

XV – Confirmatory stability tests – Tests carried out to define the conditions used in manipulating, packaging, and labeling the active pharmaceutical ingredient.

XVI – Indicative stability tests – Validated quantitative analytical methods designed to assess stability samples, able to detect alterations in the physical, chemical, or microbiological properties of a substance over time. Specific methods capable of measuring accurately the concentration of the active pharmaceutical ingredient, degradation products, and other components of interest, without interference.

CHAPTER II
TECHNICAL REGULATION

Section I
General Considerations

Article 4. The retest date or validity period of the active pharmaceutical ingredient must be determined from a long-term stability study, according to the parameters defined in this Resolution.

Article 5. The retest date or validity period must be included on the label.

Article 6. The batches to be sampled must be representative of the manufacturing process, in both pilot and industrial scales.

Article 7. It is possible to establish a provisional retest date or validity period of a maximum of 24 (twenty-four) months with minimum results from six months of accelerated study or twelve months of a long-term study.

Article 8. The stability of an active pharmaceutical ingredient must be determined before its commercialization and repeated after any significant alterations in the production processes.

Sole paragraph. Significant alterations are those related to the alteration in the retest date or validity period, conservation care, synthesis route, venue, and production process of an active pharmaceutical ingredient.

Article 9. A validity period must be established for unstable active pharmaceutical ingredients and certain antibiotics.

Article 10. The analytical methods used in the stability study must be validated and indicate stability.

Article 11. The stability studies for imported active pharmaceutical ingredients may be carried out abroad, in accordance with the parameters defined in this Resolution.

Section II
Batch selection

Article 12. The retest date or validity period of the active pharmaceutical ingredient may be based on the stability study of the pilot-scale batches.

Sole paragraph. The quality of the batches used in the stability study must be equivalent to the industrial batch.

Article 13. The accelerated and the long-term stability studies must be carried out with at least three batches of active pharmaceutical ingredients.

Section III
Packaging and labeling

Article 14. The samples intended for the stability studies of active pharmaceutical ingredients must be put in recipients with the same chemical composition and physical characteristics as the commercialization package's.

Article 15. The label and secondary package materials must not interfere in the quality of the active pharmaceutical ingredient and must ensure adequate protection against external influences and eventual contaminations.

Article 16. The storage recommendations must be included on the labels after the active pharmaceutical ingredient stability is assessed in the conditions provided for in this Resolution.

Paragraph 1. Whenever necessary, additional information must be included, such as "protect from light", "keep in a dry place", among others.

Paragraph 2. Such terms as "environment condition" or "environment temperature" must be avoided.

Paragraph 3. Temperature intervals must be supplied, particularly for the active pharmaceutical ingredient that cannot be frozen, when applicable.

Article 17. The labels must include the action to be taken in case of freezing for the active pharmaceutical ingredients that will be stored under refrigeration (2 – 8ºC).

Section IV
Specifications

Article 18. The stability study protocol must consider physical, chemical, physicochemical, biological, and microbiological assessments, when applicable.

Sole paragraph. The qualitative and quantitative presence or formation of by-products and/ or degradation products must also be assessed, using an adequate and validated methodology.

Section V
Frequency of tests

Article 19. The tests related to the accelerated stability study must be carried out at 0 (zero), 3 (three), and 6 (six) months in order to dose the active pharmaceutical ingredient, quantify degradation products and, when applicable, identify degradation products.

Sole paragraph. The other tests may be carried out only at the end of the 6 (six) months, taking the 0 (zero) moment as reference.

Article 20. The tests related to the long-term study must be carried out at 0 (zero), 3 (three), and 6 (six), 9 (nine), 12 (twelve), 18 (eighteen), and 24 (twenty-four) months in order to dose the active pharmaceutical ingredient, quantify degradation products and, when applicable, identify degradation products.

Paragraph 1. The study conducted must be presented at the end of the required retest date or validity period, taking the zero moment as reference for the other tests.

Paragraph 2. For long-term studies, the samples must be assessed at least in the periods established in the caption of this article, and annually after the second year until the retest date or intended validity period, and all specific stability assessment tests described in the approved protocol must be conducted.

Article 21. The zero moment must be defined in the stability study protocol.

Section VI
Storage Conditions

Article 22. The climate conditions to conduct the long-term stability studies are:

I – For active pharmaceutical ingredients with storage conditions of up to 30ºC, the studies must be conducted at 30ºC ± 2ºC / 75% UR ± 5% UR.

II – For active pharmaceutical ingredients with storage conditions of 2ºC to 8ºC, the studies must be conducted at 5ºC ± 3ºC.

III – For active pharmaceutical ingredients with storage conditions of -15ºC to -25ºC, the long-term studies must be conducted at -20ºC ± 5ºC.

IV – Active pharmaceutical ingredients with storage conditions below -20ºC must be dealt with on an individual basis.

Article 23. The climate conditions to carry out the accelerated stability studies are of 40ºC ± 2ºC / 75% UR ± 5% UR for active pharmaceutical ingredients with storage conditions of up to 30ºC.

Sole paragraph. The accelerated stability studies must be conducted at 25ºC ± 2ºC / 60% UR ± 5% UR for active pharmaceutical ingredients with storage conditions of 2ºC to 8ºC.

Article 24. If significant alterations occur in the results obtained in the accelerated study conditions, the retest period or validity period must be based on the long-term studies.

Article 25. If the active pharmaceutical ingredients with storage conditions of 2ºC to 8ºC yield results out of specification in the first 3 (three) months of the accelerated study, the effect of variations must be assessed in short periods, out of the recommended storage conditions, for example, during expedition or handling.

Paragraph 1. The assessment referred to in the caption of this article may be based, if appropriate, on additional tests carried out in a single batch of the active pharmaceutical ingredient for a period shorter than 3 (three) months, conducting tests more frequently than usual.

Paragraph 2. It is not necessary to continue the study up to 6 (six) months.

Article 26. The validity date or retest date shall be based only on the long-term tests for active pharmaceutical ingredients with storage conditions of -15ºC to -25ºC.

Sole paragraph. Tests must be conducted at least on a batch at a higher temperature (e.g. 5ºC ± 3ºC or 25ºC ± 2ºC), for an adequate period of time, in order to determine the effect of short intervals of the material's permanence out of the storage conditions described on the label, as it occurs, for example, during handling or transportation.

Article 27. The real storage temperature and humidity must be monitored during the stability study.

Paragraph 1. Small variations due to opening doors are considered inevitable.

Paragraph 2. The effect of variations due to equipment failure must be followed up by the person responsible for it, and its impact must be recorded and assessed in the stability study.

Article 28. The procedure to be adopted in case of freezing must be provided by the manufacturer, if such freezing is critical for the active pharmaceutical ingredient stored under refrigeration (2ºC - 8ºC).

Article 29. The stability study may be carried out considering only the temperature parameter for the active pharmaceutical ingredient stored in a package that is confirmedly impermeable to humidity.

Section VII
Follow up Studies

Article 30. The follow up studies must be carried out in the same climate conditions as the long-term study's, as provided for in this Resolution.

Article 31. A documented program must be implemented to monitor the stability characteristics of the active pharmaceutical ingredients.

Sole paragraph. The results must be used to confirm the proposed storage conditions, retest dates, or validity periods.

Article 32. The follow up study may only be conducted if the active pharmaceutical ingredient does not suffer any significant alterations after the conclusion of the long-term stability study.

Sole paragraph. In the case of a significant alteration in the active pharmaceutical ingredient, a new stability study must be conducted, as provided for in this Resolution.

Article 33. The first three commercial production batches must be included in the stability monitoring program in order to confirm the retest date or the validity period.

Sole paragraph. When the data from previous studies show that the active pharmaceutical ingredient is stable for at least 2 (two) years, less than 3 (three) batches may be used.

Article 34. At least one batch per year of active pharmaceutical ingredient produced must be added to the stability follow up study and tested in order to confirm stability, except if no batch has been produced that year.

Article 35. The follow up study must include all tests of the stability study protocol.

Section VIII
Forced Degradation Tests

Article 36. The forced degradation tests on the active pharmaceutical ingredients help to identify their probable degradation products and the analytical procedure to be adopted in the stability study, and the nature of tests depends on the type of molecule to be tested.

Sole paragraph. The study protocol must establish which tests are pertinent to the provisions stated in the caption of this article.

Article 37. The tests may be carried out on only one batch of the active pharmaceutical ingredient, and must include the effects of temperature, humidity, oxidation, light, and susceptibility to hydrolysis on a wide range of pH values.

Sole paragraph. If any of the tests mentioned is not carried out, such absence must be technically justified.

Article 38. The analysis of the degradation products generated from the degradation tests may be used to establish the degradation route and to develop the validation of the analytical methods.

Sole paragraph. It may not be necessary to assess specifically some degradation products, provided that it is confirmed that these are not formed under the conditions of accelerated and long-term stability.

Article 39. Synthesis impurities that are not degradation products do not need to be described in the stability study, but there must be an assurance that they do not interfere in the identification of degradation products.

Section IX
Photostability Studies

Article 40. Photostability studies must be conducted in order to show that exposure to light does not result in significant alterations in the active pharmaceutical ingredient.

Paragraph 1. Photostability studies may be conducted with one batch of the active pharmaceutical ingredient.

Paragraph 2. The absence of photostability studies must be technically justified, with scientific evidence that the active pharmaceutical ingredient does not suffer degradation in the presence of light.

Article 41. Photostability studies must comprise two parts: forced degradation and confirmation test.

Article 42. In forced degradation tests, the samples must be placed into chemically inert and transparent recipients.

Article 43. In forced degradation tests, various exposure conditions may be used, depending on the substance's photosensitivity and the intensity of the source used.

Article 44. For development and validation purposes, it is appropriate to limit the exposure of the active pharmaceutical ingredient and finish the tests before excessive decomposition.

Paragraph 1. The tests may be finished after an appropriate level of exposure for photostable materials.

Paragraph 2. The exposure levels used by the company must be justified.

Article 45. Under forced conditions, decomposition products may be observed, which are unlikely to be formed under the conditions used in confirmation tests.

Sole paragraph. There is no need to assess degradation products, if verified they are not formed in confirmation tests.

Article 46. If the active pharmaceutical ingredient is tested during the development phase, the photostability characteristics must be confirmed in a batch representing the production.

Sole paragraph. If the results from the confirmation test are not conclusive, the tests must be repeated with up to 2 (two) additional batches representing the production.

Subsection I
Light Sources

Article 47. The light source must be accompanied by the manufacturer's spectral specification and be in accordance with the protocol defined by the company.

Article 48. Appropriate temperature control must be kept in order to minimize its influence on test results, or a control sample may be used in the absence of light, under the same environment conditions.

Article 49. A light source similar to D65/ID65 emission standard may be used as an artificial fluorescent lamp, combining visible and UV emission.

Paragraph 1. The internationally acknowledged standard for daylight, according to definition in ISO 10977(1993), is D65.

Paragraph 2. The equivalent to indoor indirect light standard is ID65.

Paragraph 3. Filter(s) must be used to eliminate radiations, for light sources that emit significant radiation under 320nm.

Article 50. The sample may also be exposed to the combination of cold fluorescent white lamp, similar to ISO 10977(1993) and the UV fluorescent lamp with spectrum distributed between 320nm and 400nm, and maximum energy emission between 350nm and 370nm.

Sole paragraph. A significant proportion of ultraviolet light must be between 320nm and 360nm, and between 360nm and 400nm.

Article 51. Other conditions may be used in the conduction of studies, as long as they are justified.

Subsection II
Procedure

Article 52. The samples must be exposed to at least 1.2 million lux hours, integrated to an ultraviolet energy near at least 200-watt hours/m2 for confirmation studies.

Article 53. The samples may be exposed side by side, using the validated actinometric chemical system, ensuring that the exposure was guaranteed; or during an appropriate period of time, when conditions are monitored by calibrated radiometers or luxmeters.

Article 54. If the protected samples are used as controls to assess the alterations caused by the induced temperature in the process, they must be placed together with the samples being tested.

Subsection III
Sample Presentation

Article 55. Care must be taken to ensure the physical characteristics of the samples being tested are preserved, such as cooling and/ or placing the samples into sealed recipients, allowing to minimize alterations of physical state, such as sublimation, evaporation, or fusion.

Paragraph 1. The actions mentioned in the caption of this article are taken in order to establish a minimum interference with the irradiation of the samples being tested.

Paragraph 2. Possible interactions between samples and the materials used for protection or recipient components must always be considered.

Article 56. Solid samples must be placed in appropriate glass or plastic recipients, and covered, if necessary, with transparent material.

Sole paragraph. The solid samples provided for in the caption of this article must be spread, so they are not thicker than 3 mm.

Article 57. Liquid samples must be exposed in chemically inert and transparent recipients.

Subsection IV
Sample Analysis

Article 58. At the end of the exposure period in the confirmation study, the samples must be examined for any alteration of physical properties, for content and degradation products, through validated stability indication methods.

Article 59. Sampling considerations must ensure sample representativeness and homogeneity.

Sole paragraph. The analysis of the exposed sample must be carried out together with the control samples, if these are used in the test.

Article 60. Forced degradation studies must be designed to provide appropriate information for the development and validation of the test methods for confirmation studies.

Sole paragraph. The methods mentioned in the caption of this article must be capable of separating and detecting the decomposition products occurring during the confirmation studies.

Article 61. Confirmation studies must identify the necessary precautions during manufacture or formulation of the medicinal product and the need to use light-resistant package.

Section X
Report

Article 62. The stability study report must present at least the following information or the technical justification for its absence:

I – identification of the active pharmaceutical ingredient according to DCB (*Denominação Comum Brasileira* – Brazilian Common Denomination), INN (International Non-proprietary Name) or CAS (Chemical Abstract Service);

II – batch number(s);

III – batch size;

IV – specification of packaging material;

V – batch manufacturing date;

VI – initial date of the study (day/month/year);

VII – number of samples tested per batch;

VIII – number of samples analyzed per period;

IX – storage conditions;

X – frequency of tests and specifications;

XI – results from the following tests:

a) aspect;

b) content and the corresponding analytical method;

c) quantification of degradation products and the corresponding analytical method;

d) microbial limits, when applicable;

e) physical characterization;

f) physical stability; and

f) other tests carried out.

XII – conclusion.

Section XI
Assessment of Results

Article 63. The objective of the stability study is to determine a retest period or validity period applicable to all batches of active pharmaceutical ingredient that will be produced under the same circumstances.

Article 64. The retest date and the validity period are based on the assessment of the information from the stability study, including the results from physical, chemical, biological, and microbiological tests of at least three batches.

Article 65. The degree of variation in results among the batches affects the reliability on the results and the guarantee that a future batch will be completely within the specifications by the retest date, or the validity period established.

Article 66. The absence of a statistical method to assess the results must be justified.

Article 67. Any assessment must cover not only the tests carried out, but also the levels of degradation products and other appropriate items.

CHAPTER III
FINAL PROVISIONS

Article 68. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, pursuant to Law no. 6,437 of 20 August 1977, and the offender is liable to the penalties provided for by that law, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 69. This Resolution enters into force on the date of its publication.

DIRCEU BRÁS APARECIDO BARBANO