RESOLUTION – RDC NO. 45, 9 AUGUST 2012

Provides on the conduction of stability testing 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 I and II 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 the 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 testing on active pharmaceutical ingredients (APIs) 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 testing on APIs in order to predict, determine, or follow their re-test period or their shelf life.

Section I
Scope

Article 2. The manufacturers of APIs should follow the directives established in this Resolution.

Section II
Definitions

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

I – Re-test date – Date established by the API manufacturer, based on stability testing, after which the material should be re-tested to ensure that it is still adequate for immediate use, in accordance with stability tests defined by the API manufacturer, keeping the pre-established storage conditions.

II – Package – Casing, recipient, or any form of wrapping, 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 API, which may be a recipient, wrapping, or any other form of protection, removable or not, designed to pack or keep, cover or package APIs.

IV – Accelerated stability testing – Test designed to accelerate possible chemical degradation and/or physical alterations of APIs by using exaggerated storage conditions. The data obtained from these studies, in addition to long term stability studies, may be used to assess longer term chemical and physical effects at non-accelerated conditions, and to assess the impact of short exposures in conditions other than those established on the API label.

V – Long term stability testing – Test designed to verify physical, chemical, biological, and microbiological characteristics of an API and, as an alternative, after the re-test date or the shelf life. The results are used to establish or confirm the re-test date or the shelf life, and to recommend storage conditions.

VI – Impurity – Any undesired component present in the intermediary product or in the API.

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 – An API batch produced by a process equivalent to the one of industrial production batches.

XI – Shelf life or expiration date – Period of time during which the API may be used, characterized as shelf life, based on specific stability testing, 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 API due to the action of time and/or the action of external agents, such as light, temperature, pH, water, or by 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 API use and during its transportation or storage.

XIV – Forced degradation testing – Tests carried out to assess the intrinsic stability of the API as part of the development strategy, executed under more severe conditions than the ones used in the accelerated stability testing.

XV – Confirmatory stability testing – Tests carried out to define the conditions used in manipulating, packaging, and labeling the API.

XVI – Stability indicating method – 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 API, degradation products, and other components of interest, without interference.

CHAPTER II
ON THE TECHNICAL REGULATION
Section I
General Considerations

Article 4. The re-test date or shelf life of the active pharmaceutical ingredient should be determined from a long term stability testing, according to the parameters defined in this Resolution.

Article 5. The re-test date or shelf life should be included on the label.

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

Article 7. It is possible to establish a provisional re-test date or shelf life of a maximum of 24 (twenty-four) months with minimum results from six months of accelerated testing or twelve months of a long term testing.

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

Sole paragraph. Significant changes are those related to the alteration in the re-test date or shelf life, in conservation care, in the synthesis route, in the venue and production process of an active pharmaceutical ingredient.

Article 9. An expiration date must be established for labile active pharmaceutical ingredients and certain antibiotics.

Article 10. The analytical methods used in the stability testing should be validated and stability indicating.

Article 11. The stability testing 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 re-test date or the expiration date of the active pharmaceutical ingredient may be based on the stability testing of the pilot-scale batches.

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

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

Section III
Packaging and labeling

Article 14. The samples destined to the active pharmaceutical ingredient ingredient stability testing should be put in recipients with the same chemical composition and physical characteristics of the marketing package.
Article 15. The label and secondary package materials should not interfere in the quality of the active pharmaceutical ingredient, and should guarantee adequate protection against external influences and eventual contaminations.

Article 16. The storage recommendations should 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 should be included, such as “protect from light”, “keep in a dry place”, among others.

Paragraph 2. Terms such as “environment condition” or “environment temperature” should be avoided.

Paragraph 3. Temperature intervals should 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 ingredient that will be stored in refrigerators (2 - 8ºC).

Section IV
Specifications

Article 18. The protocol of the stability testing should consider physical, chemical, physical-chemical, biological, and microbiological assessments, when applicable.

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

Section V
Testing Frequency

Article 19. The tests related to the accelerated stability testing should be carried out in 0 (zero), 3 (three), and 6 (six) months and should include assay of the active pharmaceutical ingredient, quantification of the degradation products and, when applicable, identification of the 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 term studies should be carried out in 0 (zero), 3 (three), and 6 (six), 9 (nine), 12 (twelve), 18 (eighteen), and 24 (twenty-four) months and should include assay of the active pharmaceutical ingredient, quantification of the degradation products and, when applicable, identification of the degradation products.

Paragraph 1. The testing carried out should be presented at the end of the required re-test date or period of validity, taking the zero moment as reference for the other tests.

Paragraph 2. For the long term testing, the samples should be assessed at least in the periods established in the caption of this article, and annually after the second year until the re-test date or intended expiration date, and all specific stability assessment testing described in the approved protocol should be carried out.

Article 21. The zero moment should be defined in the stability testing protocol.
Section VI
Storage Conditions

Article 22. The climate condition to carry out the long term term stability testings are:

I – For active pharmaceutical ingredients with storage conditions of up to 30°C, the tests should be carried out at 30 ºC ± 2 ºC / 75% UR ± 5% UR.

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

III – For active pharmaceutical ingredients with storage conditions of -15 ºC to -25 ºC, the long term tests should be carried out at -20 ºC ± 5 ºC.

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

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

Sole paragraph. The accelerated stability testing should be carried out at 25 ºC ± 2 ºC / 60% UR ± 5% UR for active pharmaceutical ingredients with storage conditions of 2ºC to 8ºC.

Article 24. If significant changes occur in the results obtained in the accelerated testing conditions, the re-test period or expiration date should be based on the long term tests.

Article 25. If the active pharmaceutical ingredients with storage condition of 2ºC to 8ºC yield results out of specification in the first 3 (three) months of the accelerated testing, the effect of variations should be assessed in short periods, out of the recommended storage condition, 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, performing tests more frequently than the usual.

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

Article 26. The expiration date or re-test date shall be based only on the long term tests for active pharmaceutical ingredients with storage condition of - 15 ºC to - 25 ºC.

Sole paragraph. Tests should be carried out at least on a batch at a higher temperature (e.g. 5 ºC ± 3 ºC or 25 ºC ± 2 ºC), 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 occurs, for example, during handling or transportation.

Article 27. The real storage temperature and humidity should be monitored during the stability testing.

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

Paragraph 2. The effect of variations due to equipment failure should be followed by the person responsible, and its impact should be recorded and assessed in the stability testing.
Article 28. The procedure to be adopted in case of freezing should be provided by the manufacturer, if such freezing is critical for the active pharmaceutical ingredient stored in a refrigerator (2 °C - 8 °C).

Article 29. The stability testing 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 Tests

Article 30. The follow up tests should be carried out in the same climate conditions as the long term tests, provided for in this Resolution.

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

Sole paragraph. The results should be used to confirm the proposed storage conditions, re-test date or expiration date.

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

Sole paragraph. If there is a significant alteration in the active pharmaceutical ingredient, a new stability test should be carried out, as provided for in this Resolution.

Article 33. The first three commercial production batches should be included in the stability monitoring program in order to confirm the re-test date or the validity period.

Sole paragraph. When the data from previous tests 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 should be added to the stability follow up test and tested in order to confirm stability, except if no batch has been produced that year.

Article 35. The follow up test should include all tests of the stability testing protocol.

Section VIII
Tests of Forced Degradation

Article 36. The forced degradation tests on the active pharmaceutical ingredients help to identify its 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 testing protocol must establish which tests are pertinent to the provisions in the caption of this article.

Article 37. The tests may be carried out on only one batch of the active pharmaceutical ingredient, and should 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 should be technically justified.
Article 38. The analysis of the degradation products yielded in 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, as long as 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 testing, but there must be an assurance that they do not interfere in the identification of degradation products.

Section IX
Photostability Testing

Article 40. Photostability testing should be carried out in order to show that exposition to light does not result in significant alterations in the active pharmaceutical ingredient.

Paragraph 1. Photostability testing may be performed with one batch of the active pharmaceutical ingredient.

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

Article 41. The photostability testing must comprise two parts: forced degradation and confirmation test.

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

Article 43. In the 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 the confirmation tests.

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

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

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

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

Article 48. Appropriate temperature control should be kept 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 should be between 320nm and 360nm, and between 360nm and 400nm.

Article 51. Other conditions may be used when carrying out testing, as long as they are justified.

Subsection II
Procedure

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

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 should be placed together with the samples being tested.

Subsection III
Sample Presentation

Article 55. Care should 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 on 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 should always be considered.
Article 56. Solid samples should 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 should be spread, so they are not thicker than 3 mm.

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

Subsection IV
Sample Analysis

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

Article 59. Sample considerations should guarantee that they are representative and homogeneous.

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

Article 60. Forced degradation testing should be designed to provide appropriate information for the development and validation of the test's methods for confirmation tests.

Sole paragraph. The methods provided for in the caption of this article should be able to separate and detect the decomposition products occurring during the confirmation tests.

Article 61. Confirmation tests should identify the necessary precautions during manufacture or formulation of the drug and the need to use light-resistant package.

Section X
Report

Article 62. The stability testing report should present at least the following information or the technical justification of its absence:

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

II – batch number(s);

III – batch size(s);

IV – specification of packaging material;

V – batch manufacturing date(s);

VI – initial date of the test (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 testing is to determine a re-test period or shelf life applicable to all active pharmaceutical ingredient batches that will be produced under the same circumstances.

Article 64. The re-test date and the shelf life are based on the assessment of the information from the stability testing, including the results from physical, chemical, biological, and microbiological tests of at least three batches.

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

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

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

CHAPTER III
FINAL PROVISIONS

Article 68. The non-observance of the provisions in this Resolution is considered a health infraction, in the terms of Law no. 6,437 dated 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 responsibilities.

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