Regulates stability studies on active pharmaceutical ingredients

ANVISA Resolution – RDC n. 45, of August 9th, 2012

6th PART

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The board of directors from the Brazilian Health Surveillance Agency (ANVISA), in exercise of the powers conferred on it by items III and IV, from the article 15 of Law No 9.782, from January, 26th 1999, item II, and §§ 1° e 3° from article 54 of Internal Regulations, approved in the terms of Annex I of Administrative Ruling n° 354 from ANVISA, from August,11th 2006, republished on DOU (Brazilian Official Gazette) from August, 21st 2006, and its updates, considering the provisions in the items III, from article 2°, III and IV, from article 7° of law No 9.782, from 1999, and the Agency's Improved Regulatory Process Program, established by Administrative Ruling No 422, from April, 16th 2008, at a meeting held on July, 27th 2012, affirms the following Regulation from the Board of Directors and I, Director-President, order its publication:
Article 1°. *The Technical Regulation which establishes the minimum attributes for conduction of stability studies of active pharmaceutical ingredients, in the terms of this Regulation is approved.*

CHAPTER I – INITIAL PROVISIONS

Article 1°- *The Technical Regulation which establishes the minimum attributes for conduction of stability studies of active pharmaceutical ingredients with the intention of predicting, determining or monitoring its retest date or its expiration date is approved.*

Section I – Scope
Article 2°. *The facilities which manufacture active pharmaceutical ingredients must follow the guidelines established in the present Regulation*

Section II – Definitions
Article 3°. *For purposes of this Regulation, the following definitions shall be adopted:*
I – Retest date – *Period established by the ingredient's manufacturer, based on stability studies, in which the material should be retested to assure its suitability for immediate use, according to stability Tests, defined by the ingredient's manufacturer and maintained all the storage pre-established conditions.*
II – Package – *Case, container or any form of packaging, removable or not, with the intention of cover, pack, protect or keep, specifically or not, the active pharmaceutical ingredients.*
III – Primary package – *Package which is in direct contact with the active pharmaceutical ingredient, which can be a case, container or any form of packaging, removable or not, with the intention of packing or maintaining, covering or packaging active pharmaceutical ingredients.*
IV – Accelerated Stability Study – *Study designed to accelerate any possible chemical degradation and/or Physical changes in active pharmaceutical ingredients, during forced storage conditions. The collected data as well as the data from the long term studies can be used to evaluate the prolonged chemical and Physical effects in non-accelerated conditions and to evaluate the impact of short exposures to conditions other than those established on the active pharmaceutical ingredient's label.*
V – Long-term stability studies – *Study designed to verify the physical, chemical, biological and microbiological characteristics of the active pharmaceutical ingredient, and, optionally, after the retest date or the expected expiration date. The results will be used to establish or confirm the retest date or expiration date and recommend storage conditions.*
VI – Impurity – *Any undesirable component, present in the intermediary form or in the active pharmaceutical ingredient.*
VII – Active Pharmaceutical Ingredient – API – *Any substance introduced in the formulation of a drug, which, after administration to a patient, acts as an active ingredient, presenting a pharmacological activity or any other direct effect on diagnosis, cure, treatment or prevention of a disease, and affecting the structure and function of the human body.*
VIII – Intermediary – *Substance which goes under molecular changes or purification, obtained during the process stages, before being transformed into an active pharmaceutical ingredient.*
IX – Batch – *Specific amount of active pharmaceutical ingredient obtained through a process or a series of processes, so that is homogeneous, according to the specific limits. In case of continuous production, one batch can correspond to a specific fraction in the production. The batch's size can also be defined by a fixed amount or amount produced on a pre-determined period of time.*
X – Pilot scale batch – *a batch of an active pharmaceutical ingredient manufactured by a process which is equivalent to those applied to the Industrial scale batch.*
XI – Expiration Date – *Period of time in which the active pharmaceutical ingredient can be used, characterized as shelf-life and based on the specific stability studies, kept at the established storage and transport conditions.*
XII – Degradation/decomposition product – *A molecule which is a result of a chemical change in the intermediary form or in the active pharmaceutical ingredient, due to aging and/or action of external agents as light, temperature, pH, water or reaction to an excipient and/or primary package.*
XIII – Label – *Printed, lithographed, painted, heat-affixed, by pressure or self-adhesive identification, applied directly on cases, containers, packages or any other internal or external packaging, which cannot be removed or altered during API's use as well as during its transportation and storage.*

XIV – Forced Degradation Test – *Tests conducted to evaluate the active pharmaceutical ingredient's intrinsic stability as part of development strategy and executed under more rigorous conditions than those applied during the study of accelerated stability.*
XV – Tests to confirm stability – *tests conducted to define the conditions used for manipulation, packing and labeling of the active pharmaceutical ingredient.*
XVI – Stability indicating test – *Quantitative analytical methods used for analysis of stability samples, validated, capable of detecting, after a period of time, changes in the physical, chemical and microbiological characteristics of a substance. Specific methods capable of measuring, with precision, the content of an active pharmaceutical ingredient, products of degradation and other components, without interference.*

CHAPTER II – TECHNICAL REGULATION

Section I – General Considerations
Article 4°. *Retest or expiration date of an active pharmaceutical ingredient should be determined by a long-term stability test, according to the parameters defined by the present Regulation.*
Article 5°. *Retest or expiration date must be displayed on the label.*
Article 6°. *Batches to be sampled should be representative of the manufacturing process, both on pilot and industrial scales.*
Article 7°. *It is allowed to establish retest date or expiration date with a temporary period of a maximum of 24 (twenty four) months with minimum accelerated study results of six months or twelve months for long-term study.*
Article 8°. *Stability of an active pharmaceutical ingredient should be determined before marketing and repeated after any significant changes in the manufacturing process.*
Sole Paragraph. *Significant changes include those related to changes in retest or expiration date, storage conditions, synthesis method and place and manufacturing process of an active pharmaceutical ingredient.*
Article 9°. *An expiration date shall be established for unstable active pharmaceutical ingredient and specific antibiotics.*
Article 10°. *Analytical methods used for stability studies should be validated and indicative of stability.*
Article 11°. *Stability studies for imported active pharmaceutical ingredients may be conducted abroad, according to the parameters defined in the present Regulation.*

Section II - Batch Selection
Article 12°. *The retest or expiration date for the active pharmaceutical ingredient can be based on the stability study of pilot scale batches.*
Sole Paragraph. *The quality for the batches used for the stability test should be equivalent to the industrial batch.*
Article 13°. *The accelerated and long-term stability studies should be conducted with at least three batches of active pharmaceutical ingredients.*

Section III - Packing and Labeling
Article 14°. *Samples collected for the stability study for active pharmaceutical ingredients should be placed in packages with the same chemical composition and physical characteristics of the marketing packages.*
Article 15°. *Labeling material and secondary packing should not interfere in the active pharmaceutical ingredient's quality and should ensure adequate protection against external conditions and any possible contamination.*
Article 16°. *Storage conditions should be displayed in the label after the evaluation of stability for active pharmaceutical ingredient, conducted according to the conditions established on the present Regulation.*
§ 1°. *Whenever necessary, additional information shall be included such as: protect from light, keep in dry place and others.*
§ 2°. *Terms as "room condition" or "room temperature" should be avoided.*
§ 3°. *Temperature intervals should be informed, especially for the active pharmaceutical ingredient which cannot be frozen, when applicable.*
Article 17°. *Proper actions in case of freezing of active pharmaceutical ingredients which should be stored under refrigeration (2 – 8°C) must be displayed on the label.*

Section IV – Specifications
Article 18°. *The stability study protocol must have all the physical, chemical, physical-chemical, biological and microbiological evaluations, whenever appropriate.*
Sole Paragraph. *Presence or formation of by-products and/or degradation products should be evaluated, using appropriate and validated methodology.*

Section V – Frequency of tests
Article 19°. *Tests concerning the Accelerated Stability Study must be conducted at 0 (zero), 3 (three) and 6 (six) months for API's assay, quantification of degradation products and, when applicable, identification of degradation products.*
Sole Paragraph. *All the remaining tests can be conducted only at the end of 6 (six) months, considering time 0 (zero) as a reference.*
Article 20°. *Tests concerning the long term study should be conducted at times 0 (zero), 3 (three), 6 (six), 9 (nine), 12 (twelve), 18 (eighteen) and 24 (twenty four) months for assay of the active pharmaceutical ingredient, quantification of degradation product and, when applicable, identification of degradation products.*
§ 1°. *The study conducted at the end of the retest or expiration date required should be presented, having time zero as reference for all the tests.*

§ 2º. *For long term studies, the samples must be analyzed at least at the time points determined in the present article and annually after the second year, until the retest date or expiration date desired. All the specific testing described in the approved protocol should be conducted to evaluate stability.*

Article 21°. *Time zero should be defined in the stability study protocol.*

Section VI – Storage Conditions

Article 22°. *The climatic conditions for conducting long term stability studies are:*

I – *For active pharmaceutical ingredients with storage conditions up to 30 ºC, the studies should be conducted 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 conducted at 5 ºC ± 3 ºC.*

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

IV – *Active pharmaceutical ingredients with storage conditions below -20 ºC, should be considered individually.*

Article 23°. *The climatic conditions for conducting studies of accelerated stability are 40 ºC ± 2 ºC / 75% UR ± 5% UR for active pharmaceutical ingredients with storage conditions up to 30 ºC.*

Sole Paragraph. *Accelerated stability studies should be conducted 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 in the obtained results with the accelerated conditions study occur, the period for retest or the expiration date should be based on the long-term studies.*

Article 25°. *If the active pharmaceutical ingredient with storage conditions of 2ºC to 8ºC present results that are out of the specifications within the first 3 (three) months of accelerated study, the effects of variations must be evaluated, in short periods, out of the recommended storage condition, i.e., during shipment or handling.*

§ 1º. *The evaluation mentioned in the present article can be based, if appropriate, on additional tests conducted from one batch of the active pharmaceutical ingredient, for a period of time lower than 3 (three) months, with tests being conducted more often than usual.*

§ 2º. *It is not necessary to continue the study for up to 6 (six) months.*

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

Sole Paragraph. *Tests should be conducted in at least one batch exposed to a higher temperature (i.e. 5 ºC ± 3 ºC or 25 ºC ± 2 ºC), for an appropriate period of time, to determine the effect of exposure of the material for short intervals to storage conditions different from those described on the label, in conditions during shipment or handling, for example.*

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

§ 1º. *Small variations due to door opening are considered inevitable.*

§ 2º. *The effect of variations due to equipment failure must be monitored, recorded and evaluated by the professional in charge according to its impact on the stability study.*

Article 28°. *In case of freezing, the procedure to be adopted should be given by the manufacturer, if such freezing is critical for the active pharmaceutical ingredient, kept refrigerated (2 °C - 8 °C).*

Article 29°. *The stability study can be conducted considering only the temperature for the active pharmaceutical ingredient, kept on a package proven to be resistant to humidity.*

Section VII – Monitoring studies (Follow-up stability studies)

Article 30°. *The monitoring studies should be conducted on the same climatic conditions used for the long term study, recommended in the present Regulation.*

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 and retest date or expiration dates.*

Article 32°. *The study for monitoring can only be conducted if the active pharmaceutical ingredient does not suffer any significant modification after the end of the long term stability study.*

Sole Paragraph. *In case there is a significant modification on the active pharmaceutical ingredient, a new stability study shall be conducted, as recommended in the present Regulation.*

Article 33°. *The first three marketed batches must be placed in the monitoring program to confirm the retest or expiration dates.*

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

Article 34°. *At least one batch per year of active pharmaceutical ingredient produced should be added to the study of monitoring and tested to confirm stability, except if no batch was manufactured that year. Article 35. The study for monitoring should include all the tests described in the stability study protocol.*

Section VIII – Tests for forced degradation

Article 36°. *Tests for forced degradation on active pharmaceutical ingredients help identifying its probable products of degradation and the analytical*

procedure to be adopted for the stability study. The nature of the tests depend on the type of molecule to be studied.

Sole Paragraph. *It should be established in the study protocol which tests are better suited to the purpose in the caput.*

Article 37°. *The tests can be conducted in only one batch of the active pharmaceutical ingredient and the effects of temperature, humidity, oxidation, light exposure and tendency to hydrolysis at a wide range of pH values should be included.*

Sole Paragraph: *The lack of conducting any of the mentioned tests should be technically justified.*

Article 38°. *The analysis of the products of degradation generated during the degradation tests can be used for the establishment of a degradation pathway and the development for the validation of analytical methods.*

Sole Paragraph. *It may not be necessary to specifically evaluate some products of degradation; as long as it is proven that they are not formed under the accelerated stability and long term conditions.*

Article 39°. *Synthesis impurities which are not product of degradation do not need to be described in the stability study; however, it must be assured that they do not interfere in the identification of the products of degradation.*

Section IX – Photostability Studies

Article 40°. *Photostability Studies should be conducted with the purpose of showing that light exposure does not promote significant modifications on the active pharmaceutical ingredient.*

§ 1º. *Studies of photostability may be conducted with one batch of active pharmaceutical ingredient.*

§ 2º. *The lack of photostability study should be followed by a technical reason, with proven scientific evidence that the active pharmaceutical ingredient does not suffer degradation in the presence of light.*

Article 41°. *Photostability study must be composed of two parts: forced degradation and confirmatory test.*

Article 42°. *In forced degradation studies, samples should be placed on transparent and chemically inert containers.*

Article 43°. *In forced degradation studies, a variety of exposure conditions may be used, depending upon substance photosensibility and light intensity used.*

Article 44°. *For development and validations purposes, it is appropriate to limit the exposure of the active pharmaceutical ingredient and finish the study prior to excessive decomposition.*

§ 1º. *For photostable materials, studies may be finalized after an appropriate level of exposure.*

§ 2º. *Levels of exposure used by each company should be justified.*

Article 45°. *It can be observed, at forced conditions, products of decomposition, which are unlikely to be formed under circumstances used for the confirmatory tests.*

Sole Paragraph. *It is not necessary to evaluate the degradation products in case it is observed they were not formed during the confirmatory studies.*

Article 46°. *If the active pharmaceutical ingredient is tested during the development phase, the photostability characteristics must be confirmed on a representative batch of the production.*

Sole Paragraph. *If the results obtained with the confirmatory study were not conclusive, the tests should be repeated with up to 2 (two) additional batches, representative of the production.*

Subsection I – Sources of light

Article 47°. *The source of light should be accompanied by the manufacturer's spectrum specification and according to the protocol defined by the company manufacturer.*

Article 48°. *An appropriate temperature control should be kept, in order to minimize its influence on the test results, or a control-sample can be used in the absence of light, but same environment conditions.*

Article 49°. *A source of light similar to the D65/ID65 emission pattern can be used, as an artificial fluorescent lamp combining visible and UV emissions.*

§ 1º. *The international standard accepted for day light, according to ISO 10977(1993), is D65.*

§ 2º. *The equivalent to indirect light of interiors is ID65.*

§ 3º. *A filter(s) should be used, in order to eliminate radiations to the source of light emitting significant radiation below 320nm.*

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

Sole Paragraph. *A significant range of the UV light should be between bands 320 and 360 nm and between 360 and 400 nm.*

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

Subsection II – Procedure

Article 52°. *Samples should be exposed to, at least, 1.2 million of lux hours, integrated to UV energy next to, at least, 200 Watt hours/m2 for confirmatory studies.*

Article 53°. *Samples may be exposed side by side, using a validated actinometric chemical system, ensuring exposure; or the period of time appropriate when conditions are monitored by calibrated radiometers or luximeters.*

Article 54°. *In case protected samples are used as controls for evaluation of changes caused by the influence of temperature, they should be kept together with the tested samples.*

Subsection III – Sample presentation

Article 55°. *Precautions should be taken to assure that all physical characteristics of the tested samples are preserved, such as refrigeration and/or sample*

positioning on sealed containers, minimizing any alteration of the physical state such as sublimation, evaporation or fusion.

§ 1º. *The actions mentioned in this caput are taken with the intention of establishing a minimum amount of interference with the irradiation of the tested samples.*

§ 2º. *Possible interactions between samples and materials used for its protection or containers components must always be considered.*

Article 56°. *Solid samples should be placed in appropriate glass or plastic covered containers, if necessary, with a transparent material.*

Sole Paragraph. *Solid samples mentioned in this caput should be spread on a layer with a width not exceeding 3 mm.*

Article 57°. *Liquid samples should be exposed in transparent and chemically inert containers.*

Subsection IV – Sample analyses

Article 58°. *At the end of the exposure period in the confirmatory study, the samples should be examined for any alteration of physical properties, for content and for products of degradation, by validated and indicative methods of stability.*

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

Sole Paragraph. *Analyses of the exposed sample should be done concomitantly with the control samples, in case they are included in the test.*

Article 60°. *The forced degradation studies should be designed to provide appropriate information to the test's method development and validation for confirmatory studies.*

Sole Paragraph. *Methods mentioned in this caput should be capable of separating and detecting products of decomposition that eventually appear during the confirmatory studies.*

Article 61°. *Confirmatory studies should identify all needed precautions during manufacturing or formulation of a drug and the need for a light resistant package.*

Section X – Report

Article 62°. *The stability study report should present at least, the following information or technical reason for its absence:*

I – *Active pharmaceutical ingredient's identification by DCB (Brazilian Common Denomination), INN (International Non-proprietary Name) or CAS (Chemical Abstract Service);*

II – *Batch(s) number(s);*

III – *Batch(s) size (s);*

IV – *Specification of storage material;*

V – *Batch(s) manufacturing date;*

VI – *Date of beginning of the study (day/month/year);*

VII – *Number of samples tested per batch;*

VIII – *Number of samples analyzed per period;*

IX – *Storage conditions;*

X – *testing frequency and specifications;*

XI – *results from the following tests:*

a) *aspect;*

b) *content and corresponding analytical method;*

c) *Quantification of degradation products and corresponding analytical method;*

d) *microbial limits, when appropriate*

e) *physical characterization*

f) *Physical stability; and*

f) *additional tests conducted.*

XII – *conclusion.*

Section XI – Evaluation of results

Article 63°. *The purpose of the stability study is to determine a retest period or an expiration date applicable to all active pharmaceutical ingredient's batches, manufactured under the same circumstances.*

Article 64°. *The retest and expiration date are based on the evaluation of the data obtained from the stability study, including the results from the physical, chemical, biological and microbiological tests, from at least three batches.*

Article 65°. *The level of variation among batches affects the results reliability and assures that future batches will be entirely within the specifications of the attributed retest or expiration dates.*

Article 66°. *The lack of use of statistical analysis to evaluate the results shall be justified.*

Article 67°. *Any evaluation must cover not only the conducted tests, but also degradation products and other appropriate attributes.*

CHAPTER III – FINAL PROVISIONS

Article 68°. *The non-compliance of the provisions in the present Regulation will be construed as violation of sanitary nature, in the terms of law No 6437 dated August 20th 1977, submitting the violator to the prescribed penalties without prejudice of civil, administrative and criminal responsibilities.*

Article 69°. *This Regulation takes effect on the date of its publication.*

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