

RESOLUTION – RE Nº 1, OF JULY 29TH 2005

Brazilian Federal Register 08/01/2005

The Director of the Brazilian Health Surveillance Agency, exercising the powers conferred to him by law, and considering art. 111, subsection II, subparagraph "a" ANVISA Internal Regulation approved by Ordinance No 593, of August 25th 2000, reissued on December 22nd, establishes:

Art. 1 Authorization *ad referendum* of the publication of the Guide for Stability Studies, attached.

Art. 2 Resolution - RE No 398, of November 12th 2004, published in the Brazilian Federal Register of November 16th 2004, is revoked.

Art. 3 This Resolution is in force as of the date of its publication.

DIRCEU RAPOSO DE MELLO

ATTACHMENT – GUIDE FOR STABILITY STUDIES

The stability of pharmaceutical products depends on environmental factors such as temperature, humidity, light, and others factors related to the product itself, such as physical-chemical properties of the active ingredients and pharmaceutical excipients, pharmaceutical form, manufacturing process, type and properties of the packing materials.

APPLICABILITY

Guide for conducting stability studies of pharmaceutical products so as to estimate, determine or follow-up their shelf lives.

1. DEFINITIONS

ACCELERATED STABILITY STUDY

Study developed to accelerate the chemical degradation and/or physical changes of a pharmaceutical product in storage imposed conditions. The data obtained, together with the data from long-term studies, may be used to assess the prolonged physical/chemical effects under non-accelerated conditions and to assess the impact of short-term expositions to conditions which are not the ones established in the label of the product and that may be present during transportation.

FOLLOW-UP STABILITY STUDY

Study conducted to evaluate if the pharmaceutical product maintains its physical, chemical and microbiological characteristics according to the results obtained in the long-term stability studies.

LONG-TERM STABILITY STUDY

Study developed for the evaluation of the physical, chemical, biological, and microbiological characteristics of a pharmaceutical product during, and – optionally – after the expected shelf-live. The results are used to establish or confirm the shelf life and to establish storage conditions.

BATCH

Quantities of a product obtained in a single process or series of processes, whose essential characteristics are homogeneity and quality within the specified limits.

PILOT SCALE BATCH

A batch of a pharmaceutical product manufactured by means of a completely representative process which simulates the industrial production batch and which is established by a minimum amount corresponding to 10% of the expected batch, or quantity equivalent to the minimum capacity of the industrial equipment to be used.

SHELF LIVE

Expiry date for the use of a pharmaceutical product established by the manufacturer based on its specific stability studies, and kept under the established storage and transportation conditions.

STABILITY STUDIES

Set of studies developed to get information about the stability of the pharmaceutical products aiming at defining its expiry date and shelf life in specified packing and storage conditions.

2. GENERAL DISPOSITIONS

2.1 The shelf life of a product to be marketed in Brazil is determined by a long-term stability study according to the parameters set forth in the table below. At the time of registration, the product may be granted a provisory shelf-life corresponding to 24 months if the report of long-term stability study of 12 months or the report of the 6 months accelerated stability study – together with the preliminary results of the long-term study - have been approved, according to the parameters set forth in the table below.

Pharmaceutical Form	Storage Condition*	Package	Temperature and Humidity Accelerated **	Temperature and Humidity Long-Term**
Solid	15°C –30°C	Semi-permeable	40°C ± 2°C / 75% UR ± 5% UR	30°C ± 2°C / 75% UR ± 5% UR
Solid	15°C –30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
Semi-solid***	15°C –30°C	Semi-permeable	40°C ± 2°C / 75% UR ± 5% UR	30°C ± 2°C / 75% UR ± 5% UR
Semi-solid	15°C –30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
Liquids	15°C –30°C	Semi-permeable	40°C ± 2°C / 75% UR ± 5% UR	5% UR / 75% UR ± 5% UR
Liquids	15°C –30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
Gases	15°C –30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
All pharmaceutical forms	2°C –8°C	Impermeable	25°C ± 2°C	5°C ± 3°C
All pharmaceutical forms	2°C –8°C	Semi-permeable	20°C ± 2°C / 60% UR ± 5% UR	5°C ± 3°C
All pharmaceutical forms	-20°C	All	-20°C± 5°C	-20°C± 5°C

* Any storage recommendation in temperatures within these ranges must be mentioned in the package inserts and labels. The recommended temperature does not exempt the product from the stability studies within the temperatures established in the last two columns of the table.

** The temperature and humidity values are fixed and the variations are due to expected oscillations in the climatic chamber and possible openings for removal or entry of material.

*** The study for water-based liquid and semi-solid products must be conducted at 25% RH or 75% RH. If the study is conducted at 75% RH, the weight loss value must be multiplied by 3.0.

2.2. The shelf life must be confirmed by presenting a 24-months long term stability study, registered as complementary information to the process. This document is required for the register renewal.

2.3. The stability study must be conducted with the pharmaceutical product in its primary package.

2.4. To be released by the health authority at harbors and airports, the bulk imported products must show in their labels the manufacturing date, expiry date and storage conditions up to the transfer to the primary package. The study will be assessed during inspection in the manufacturing company.

2.5. For imported products, the stability studies may be conducted abroad according to the parameters set forth in this Resolution. In case of bulk imported products, the expiry date must consider the maximum storage time up to the transfer to the primary package.

2.6. For imported products – bulk or in their primary package - the follow-up stability studies must be conducted in Brazil according to the parameters set forth in this Resolution

2.7. Additional studies - such as photosensitivity - that may be pertinent according to the characteristics of the product, may be required for proving the stability of the pharmaceutical product. For these cases, we suggest following the technical recommendation available at Anvisa's portal. The non-presentation of photosensitivity studies must be followed by the technical justification with scientific evidences that the active ingredient(s) is not affected by light or that the primary package does not allow the entry of light.

2.8. The use of summarized models of stability studies based on the principles set forth in the technical recommendation available at Anvisa's portal is allowed.

2.9. All stability study reports – regardless of the pharmaceutical form – must present the following information or technical justification for absence:

Description of the product and specification of the primary package

Batch number of each batch involved in the study

Manufacturer's description of the active ingredients

Appearance

Study plan: material, methods (design) and schedule.

Start date of the study

Amount of active ingredient and corresponding analytical method

Quantification of degradation products and corresponding analytical method

Microbiological limits

The company must add the following information or technical justification of absence for every solid pharmaceutical product:

Dissolution

Hardness

The company must add the following information or technical justification of absence for the liquid and semi-solid pharmaceutical products:

Ph

Sedimentation rate after agitation in suspensions

Clearness in solutions

Phase separation in emulsions and creams

Loss of weight in water-based products

2.10. The accelerated stability report or 12-months long term report which presents a variation equal to or lower than 5.0% of analysis value of the batch release will be approved for purposes of the provisory 24 months shelf life.

If the dosing variations are between 5.1% and 10.0% in the accelerated stability study, the provisory shelf life will be reduced to 12 months. The dosing at time zero may not be higher than the product specifications according to the pharmacopoeia approved by Anvisa or, in the absence of pharmacopoeic information, the method validated according to the Guide for validation of analytical and bioanalytical methods.

If the specification in the pharmacopoeia and/or validated method allows time zero to be 10% higher than the value informed, the loss variation will be analyzed according to the specific case.

2.11. For definitive shelf life, only the stability report presenting the dosing variations of active ingredients within the specifications set forth in the Pharmacopoeias and/or product methods validated according to the Guide or validation of analytical and bioanalytical methods will be approved.

2.12. In case of products that need reconstitution or dilution, the initial and final information proving the period of use during which the product is stable after reconstitution - and under the specified storage conditions - must be presented. The studies must be conducted using the diluent specified for reconstitution of the pharmaceutical product. If more than one diluent may be used, the study must be conducted with the one that presents the less stable pharmaceutical product.

2.13. In case of effervescent tablets, the initial and final information proving the period of use during which the product is stable after opening of the primary package - and under the specified storage conditions - must be presented. These studies must be conducted according to the parameters and tests set forth in this Resolution.

2.14. Exceptionally for those products that must be stored under 25°C and which are of exclusive use in hospitals and medical clinics, stability studies for the conditions specified for Zone II (25°C/60%UR) will be accepted, once that it has been proven that the product does not bear the conditions established in this Resolution. However, the owner of the register must assure the recommended conservation conditions during transportation and distribution.

3. BATCH SELECTION

3.1. For registration and post-registration changes purposes, in the accelerated and long-term stability studies: one or three batches, according to the pertinent laws and regulations.

3.2. The batches to sampled must be representative of the manufacturing process, both in pilot and industrial scale.

3.3. For those products whose concentration of active ingredients are below 0.99 milligram per dosing unit, pilot batches with quantities below the industrial batches are not allowed. Not applicable to solutions.

3.4. The follow-up studies must be conducted according to the climatic conditions set forth in this Guide. The sampling must be according to the parameters described as follows:

- a) One annual batch, for production above 15 batches/year.
- b) One batch every two years, production below or equal to 15 batches/year.
- c) For products of different concentrations and proportional formulations, the one that presents the highest number of batches produced by year may be used as the selection criteria.

3.5. The follow-up study may only be conducted if the product does not suffer any changes after the end of the long-term stability study. If any changes are made to the product, a new stability study must be conducted according to this Guide.

4. TEST FREQUENCY

4.1. Accelerated study: 0, 3 and 6 months for dosing, quantification of degradation products, dissolution (when applicable), and pH (when applicable). For the remaining tests, present a study 6 months after time zero.

4.2. Long-Term Study: 0, 3, 9, 12, 18 and 24 months for dosing, quantification of degradation products, dissolution (when applicable), and pH (when applicable). For the remaining tests, present a study at the expiry date required after time zero.

4.3. Follow-up study: every 12 months, all the tests of a stability study report must be conducted. The report must be made available at the inspection.

5. ADEQUACY

5.1. The presentation of stability studies is mandatory at the time of the first register renewal after the publication of this Resolution if such studies are not part of the registration documents, even if they have been conducted according to the parameters in force as of the beginning of the studies.

5.2. At the time of registration, post-registration or registration renewal - up to July 31st 2007 - Anvisa will accept on-going long-term stability studies with humidity parameters below 75% , However, the climatic chambers must be pre-qualified for a humidity of 75% as from the publication of this Resolution. The company decides whether to reinitiate or not these studies.

5.3. If the long-term stability studies have been conducted only with humidity parameters different from the ones set forth in this Resolution; at the first renewal after August 1st 2007, the companies must present follow-up stability studies in one batch according to this Resolution. For products complying with these circumstances, the renewal time is between August 1st 2007 and July 31st 2008, and for those whose shelf life is equal to or higher than 36 months, it is possible to approve a shelf life of 36 months if studies of at least 24 months are presented.

5.4. If the long-term stability studies have been conducted only with temperature and humidity parameters different from the ones set forth in this Resolution; at the first renewal after August 1st 2007, the companies must present 12 month long-term stability studies, or 6 months accelerated study followed by the respective long-term study according to this Resolution. If stability conditions have not been proven at the time of the register renewal, the company will be asked to stop marketing the product to keep the register; otherwise the register will not be renewed.

5.5. If long-term stability studies, conducted according to the conditions of this Resolution, prove a shelf life inferior to the one established in the product register, the company must immediately and provisory implement and request post-registration change in the shelf life based on the data obtained.