Title

Stability tests specification for cosmetics products according to ANVISA- BRAZIL – Volume 2

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□ Abstract

The proposal of this article is to expresses Anvisa's understanding of procedures, routines and methods deemed adequate to comply with the technical requirements for stability studies in cosmetics products. The information to be found in the present publication, without any intention of exhausting the proposed theme, proposes to suggest to professionals, orientations for the investigation of those procedures involved in quality related to stability studies of cosmetic products, and according to the needs of each company. This is the second one of a series of 3 complementary papers.

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1. Introduction

It is the responsibility of companies to assess the stability of their products before putting them before the consumer and this is a fundamental requirement for the quality and safety of the products. Products that are exposed to consumption and that present organoleptic, physical-chemical and or microbiological stability problems, not only fail to comply with the technical quality requirements but may furthermore, put consumer health at risk which constitutes a health infraction.

The presentation of information on stability, required in the act of the regularizing the product or by the sanitary authority when conducting inspections, is established in the current legislation. Besides that, what is set out in the Term of Responsibility signed by the company wherein the company declares itself as having data that certifies the effectiveness and the safety of its products, must be complied with.

According to the stability profile of a product, it is possible to assess performance, security and effectiveness as well as its acceptance by the consumer. The stability study of a product supplies indications about the behavior of the product over determined time intervals whilst facing the environmental conditions to which it may be exposed from the production date until the expiry date.

According to the monograph of the International Federation of Societies of Cosmetic Chemists – IFSCC, the stability test is considered a predictive procedure, based on information obtained from products stored in conditions that are intended to accelerate alterations that are liable to happen in market conditions. As in all predictive procedure the results are not absolute, but have a probability of success.

Due to the competitiveness that characterizes the companies of the sector and to the nonexistence of specific standardized rules for the cosmetics industry, professionals working in this field have used as their references, stability studies used by the pharmaceutical industry with appropriate adaptations.

Finally, in order to have an understanding of the proposed guidelines included in this Guide, all the definitions, analytical specifications and or general instructions, which have to do with stability studies of cosmetic products, must take into account their adaptation to the particular characteristics of each company.

2. Accommodating The Samples

It is recommended that samples for the evaluation of stability be placed in neutral, transparent glass flasks with a lid that assures good closing, avoiding gas or vapor losses to the environment. The quantity of product must be sufficient for the necessary appraisals. In the case of a known incompatibility between the components of the formulations and glass, the formulator must chose another containing material. The use of other materials is at the criterion of the formulator, depending on his acquired knowledge regarding the formulation and the containing material.

The incorporation of air in the product must be avoided during placement in the test recipient. It is important not to fill the total volume of the package, allowing a head space of approximately one third of the capacity of the flask for possible gaseous exchanges.

The final containing material may be used parallel to the neutral glass thus anticipating the appraisal of compatibility between the formulation and the package material.

3. Storage Conditions

The climatic characteristics of the zone where the products are to be produced and/or commercialized, as well

as the transport conditions to which they will be submitted must be considered.

For the stability tests, the most common storage conditions for samples to be considered are: temperature of environment,(high, low), exposure to light and freezing and defrosting cycles.

- Temperature of the environment

Samples stored in a temperature-monitored environment.

- High temperatures

The temperature limits most frequently used during product development are:

- Oven: T = 37 ± 20 C
- Oven: T = 40 ± 20 C
- Oven: T = 45 ± 20 C
- Oven: T = 50 ± 20 C

Under these conditions the occurrence of physical-chemical alterations is frequent, thus the obtained results must be evaluated carefully.

- Low temperatures

The limits of temperature most used during the development of products are:

- Refrigerator: T = 5 ± 20 C
- Freezer: T = -5 ± 20 C or T = -10 ± 20 C

- Light radiation exposure

This may significantly alter the color and the odor of the product and lead to the degradation of formulation ingredients. In conducting the study, the light source can be sunlight captured through glass panels specially designed for the purpose or lamps that have an emission spectrum similar to that of the sun, such as xenon lamps. Ultraviolet light sources are also used.

- Freezing and defrosting cycles

To test this condition the samples are stored in alternated temperatures at regular time intervals. The number of cycles is variable. Suggested limits:

- Cycles of 24 hours at room temperature and 24 hoursat-5 ± 20 C.
- Cycles of 24 hours at 40 ± 2° C and 24 hours at 4 ± 20 C.
- Cycles of 24 hours at 45 ± 2° C and 24 hours at -5 ± 20 C.
- Cycles of 24 hours at 50 ± 2° C and 24 hours at -5 ± 20 C.

4. Stability Studies

4.1 Preliminary Stability Test

This test is also known as the Screening Test, Accelerated Stability test or Short Term test is aimed at assisting and orientating the choosing of formulations.

The study of preliminary stability consists of making the test in the initial phase of product development using different laboratory formulations and with a reduced duration. It uses extreme temperature conditions with the objective of accelerating possible reactions among the components and the appearance of signs that must be observed and analyzed according the specific characteristics of each type of product. Due to the conditions under which it is conducted, this study does not have the goal of estimating the life cycle of the product but rather that of helping in the screening of formulations.

It is recommended that samples for the evaluation of stability be placed in neutral, transparent glass flasks with a lid that assures good closing, avoiding gas or vapor losses to the environment. The quantity of product must be sufficient for the necessary appraisals. In the case of a known incompatibility between the components of the formulations and glass, the formulator must choose another containing material.

The use of other materials is at the criterion of the formulator, depending on his acquired knowledge regarding the formulation and the containing material. The incorporation of air in the product must be avoided during placement in the test recipient. It is important not to fill the total volume of the package, allowing a head space of approximately one third of the capacity of the flask for possible gaseous exchanges.

The final containing material may be used parallel to the neutral glass thus anticipating the appraisal of compatibility between the formulation and the packaging material.

The duration of the study is generally fifteen days and helps in the screening of the formulations. The formulations under test are submitted to stress conditions aimed at accelerating the appearance of signs of possible instability. Generally the samples are submitted to heating in ovens, cooling in refrigerators and to alternated cooling and heating cycles.

- The values generally adopted for elevated temperatures can be:
  - Oven: T = 37 ± 20 C
  - Oven: T = 40 ± 20 C
  - Oven: T = 45 ± 20 C
  - Oven: T = 50 ± 20 C
- The values generally adopted for low temperatures can be:
  - Refrigerator: T = 5 ± 20 C
  - Freezer: T = -5 ± 2o C or T = -10 ± 20 C.
- The values generally adopted for the cycles are:
  - Cycles of 24 hours at 40 ± 20 C, and 24 hours at 4 ± 20 C - during four weeks.
  - Cycles of 24 hours at 45 ± 2o C and 24 hours at –5 ± 20 C – during 12 days (6 cycles).
  - Cycles of 24 hours at 50 ± 2o C and 24 hours at – 5 ± 20 C – during 12 days (6 cycles).

In this type of study, the samples are stored under different temperature conditions for regularly alternated time intervals.

The periodicity of the sample evaluations can vary according to technical experience,specifications of the product, the special characteristics of a certain component of the formulation or the preserving system that is used, however what is most usual in this preliminary study is for evaluation to be made at the very beginning and then during all the days in which samples are submitted to the study conditions.

The parameters that are generally evaluated must be defined by the formulator and depend on the characteristics of the formulation undergoing study and those of the components used in the formulation. The evaluation generally is of:

- Organoleptic characteristics:
  - appearance, color, odor and flavor, whenever applicable.
- Physical-chemical characteristics:
  - pH value, viscosity, density, or others.

A reference sample must also be taken, also denominated as the standard sample, which generally can be kept in the refrigerator or at room temperature, protected from light. In a complementary manner, samples from the market of products with a known acceptability or of other similar products deemed to be satisfactory in relation to the parameters being evaluated.

4.2 Accelerated Stability

Also known as normal or exploratory stability, has the object of providing data to foresee the stability of the product, its useful life span, and the compatibility of the formulation with the containing material.

4.2.1 General Considerations

This test is applied also in the development phase of the product batches on a laboratory scale and to pilot manufacturing batches and the test may be extended to cover the initial production. It generally uses less extreme conditions than the previous test. It serves as an auxiliary in the determining of formulation stability.

It is a predictive study that can be used to estimate the expiry date of the product. It can also be carried out whenever there are any significant alterations made to ingredients of the product and/or the manufacturing process, or to containing material that comes into direct with the product, or in order to validate new equipment or outsourced manufacture.

4.2.2 Procedure

It is recommended that samples for the evaluation of stability be placed in neutral, transparent glass flasks with a lid that assures good closing, avoiding gas or vapor losses to the environment. The quantity of product must be sufficient for the necessary appraisals. In the case of a known incompatibility between the components of the formulations and glass, the formulator must chose another containing material. The use of other materials is at the criterion of the formulator, depending on his acquired knowledge regarding the formulation and the containing material.

The incorporation of air in the product must be avoided during placement in the test recipient. It is important not to fill the total volume of the package, allowing a head space of approximately one third of the capacity of the flask for possible gaseous exchanges.

The final containing material may be used parallel to the neutral glass thus anticipating the appraisal of compatibility between the formulation and the package material.

The compatibility of the containing material with the formulation will be discussed under topic 4.4.
The duration is generally of ninety days and the test formulations are submitted to conditions less extreme than in the Preliminary Stability Test. In some cases, the duration of this test can be extended for six months or even one year, depending on the type of product. The samples can be submitted to heating in ovens, cooling in refrigerators, exposure to light radiation and to the environment.

- The values generally adopted for elevated temperatures can be:
  - Oven: T = 37 ± 20 C
  - Oven: T = 40 ± 20 C
  - Oven: T = 45 ± 20 C
  - Oven: T = 50 ± 20 C
- The values generally adopted for low temperatures can be:
  - Refrigerator: T = 5 ± 20 C
  - Freezer: T = -5 ± 20 C, or T = -10 ± 20 C

- Exposure to light radiation

This may significantly alter the color and the odor of the product and lead to the degradation of formulation ingredients. In conducting the study, the light source can be sunlight captured through glass panels specially designed for the purpose or lamps that have an emission spectrum similar to that of the sun, such as xenon lamps. Ultraviolet light sources are also used.

The samples must also be submitted to Accelerated Stability Test accommodated in the containing material.

The products must be stored under more than one temperature condition, so that behavior can be evaluated for the many environments to which they may be submitted.

The periodicity of the sample evaluations can vary according to technical experience, specifications of the product, the special characteristics of a certain component of the formulation or the preserving system that is used, however what is most usual in the accelerated study is for evaluation to be made at the very beginning, after 24 hours and then on the 7th, 15th, 30th, 60th and 90th days. If the study is to be extended then a monthly evaluation is recommended until the end of the study.

The parameters to be evaluated must be defined by the formulator and depend on the characteristics of the product that is being studied and on the ingredients being used in the formulation. Generally they are:

- organoleptic parameters: appearance, color, odor and flavor, whenever applicable;
- physical-chemical parameters: pH value, viscosity, density, among others;
- microbiological parameters: microbial count and challenge test of the preserving system made before and/or after the accelerated study period.

A reference sample must also be taken, also known as a standard sample, which generally can be kept in the refrigerator or at room temperature, protected from light. In a complementary manner, samples from the market of products with a known acceptability or of other similar products deemed to be satisfactory in relation to the parameters being evaluated, may be used as standards.

4.3 Shelf Test

The aim of the Shelf Test also known as the Long-term Stability Test, is to validate the stability limits of the product and to test the expiry date estimated using the accelerated stability test.

This study is carried out over a period equivalent to the time of expiry estimated during the stability studies previously mentioned. It is used to evaluate the behavior of the product under normal storage conditions. The frequency of the analyses must be determined according to the product, the number of the batches produced and the estimated expiry date, and if the intention is to extend the expiry period then the follow up process can be continued.

In the shelf stability study, the representative samples of the product are stored at room temperature. The number of samples must be sufficient to allow for the carrying out of all the tests foreseen in the study. These samples are analyzed periodically up until the expiry date.

The same tests suggested in the previously mentioned procedures must be done and others may be defined by the formulator according to the characteristics of the formulation.

4.4 Test of Compatibility Between Formulation and Containing Material

The stability of the product and its compatibility with the containing material are distinct concepts, separate and complementary, that must be applied to the product before it is commercialized.

In this test, several alternative containing materials are analyzed to determine which is most suitable for the product.

The environmental conditions and the periodicity of the analysis can be the same as those mentioned for the formulation Stability Studies and in this phase possible interactions between the product and the containing material which comes into direct contact with it are identified. Phenomena such as: absorption, migration,

corrosion and others that may impair its integrity, can be observed.

Considering that this kind of test is commonly destructive, it's necessary to define the number of samples to be tested with certainty.

4.4.1 Types of Containing Material and Main Evaluations

Cellulose Packaging

Examples: cartridges, trays, displays and cardboard packages.

What is evaluated:

- alterations in the paper and formulation structure, checking for possible migration of components that could contaminate the product (e.g.: sachets);
- physical-chemical stability of the packaging;
- alterations in the formulation – appearance, color, odor, among others;
- appearance and functionality of the package;
- barrier function (ex: permeation of oil, water or gases);
- metal determination, whenever applicable.

Metal Packaging

What is evaluated:

- delamination, when applicablel;
- corrosion;
- alterations in the formulation – appearance, color, odor, among others;
- appearance and functionality of the package;
- formula reaction;
- polish or resin integrity (internal and external);
- metal determination, whenever applicable;
- functionality.

Plastic packaging

Types of plastic: Polypropylene (PP), high density Polyethylene (PEAD), low density Polyethylene (PEBD),

Polyethylene Terephthalate (PET), Polystyrene (PS) and Poly vinyl chloride (PVC).

What is evaluated:

- alterations in the formulation – appearance, color, odor, among others;
- appearance and functionality of the package;
- interaction and migration of components between package and product;
- porosity to water vapor;
- light transmission;
- heat-sealing (whenever applicable);
- deformity (collapse or bending).

Glass packaging

What is evaluated:

- alterations in the formulations – appearance, color, odor, among others;
- appearance and functionality of the package;
- mechanical resistance of the package.

Pressurized packaging

The evaluations must be in conformity with the characteristics of the previously related materials and also consider the influence of the propellant on the formulation and on the package materials.

What is evaluated:

- performance of the product in accordance with its functionality;
- corrosion and electrolysis of the package;
- internal and external polish control (porosity), whenever applicable;
- homogeneity of coatings and linings - bubble formation, fissures and corrosion;
- performance of the valve and it's components;
- presence of electrolytes, odor and formulation precipitation.

4.5 Distribution and Transportation Test

The stability studies aim to predict product behavior throughout the logistics system, including transportation

and handling.

The conditions to which the products are submitted during transportation can affect the stability of the formulations, and in some cases, separation of phases (emulsions), diminishment of gel viscosity or compacting of suspensions, among others, may occur. An aggravating factor for this effect is elevated temperature during the transportation of the product.

The combination of product and package is the first aspect that the customer will see. The package aggregates value to the product, offering protection and communication, besides maintaining the characteristics of the same.

The maintenance of the characteristics of the product in its package is a valuable aspect, since any problem in this direction may impair all the aggregated value.

In this context, a transportation test program must be established, to be applied at two moments. The first is to determine the package's capacity to resist the stress conditions normally existing in handling and transportation. This step is applied in the development phase of a new package or of a new containing material. At a second moment, the test is applied to evaluate the stability of this combination when facing various real handling, transportation and storing conditions.

4.5.1 Types of Transportation Tests

Real Test – the samples are submitted to certain real conditions of the means of transport (truck, airplane, train, ship) evaluating: primary package, secondary package, final containing material and formulation. As variables that influence in the process we have: temperature, vibration, humidity, pressure and impact.

Simulated Test – the samples are submitted to conditions and equipments that simulate different types of means of transport and their variations. This test cannot show, in some cases, the reality that the product will be subjected to, but it is used as a previous evaluation to determine the probability of the package's performing properly during real transportation. The simulation conditions involve: vibration, pressure, drop test and environmental variations (humidity and temperature).

For these tests, the American Society for Testing & Materials (ASTM) can be sourced or they may be done according to the internal procedures of the company

4.5.2 Evaluated Characteristics

In regard to the packaging, the following are evaluated: sealing capacity, risks, breaking and damage to package components and alterations that impair its integrity and appearance.

In regard to the formulation, the following are evaluated: organoleptic characteristics, viscosity, pH value, fusion point and other parameters depending on the characteristics of the product.

Transportation of a complete load generally provokes less damage than the transportation of a fractionated load in which the packages are handled repeatedly during the operations and have a lot more chances of falling or being put next to other potentially damaging loads.

4.5.3 The Kinds of Forces That May Affect the Products During Distribution and Transportation

In railway transportation, damage may occur due to the changing or coupling of the wagons.

In sea transportation the products are submitted to elevated humidity levels, vibration and salinity.

In air transportation the products are submitted to drastic temperature and pressurization conditions.

In highway transportation the products can be submitted to drastic temperature, humidity and vibration conditions.

The complete or fractioned load set up alters the handling characteristics including falling probabilities and/or contamination.

Companies that use varied distribution channels must evaluate the conditions to which the products will be submitted especially in Brazil, where the main means of transportation is the highway. It is important to establish and implement Good Distribution and Transportation Practice in order to maintain the initially proposed characteristics of the products.

The characteristics of the storing place also determine the environmental conditions (temperature and humidity), the piling height, the probability of insect and pest infestations and dust accumulation.

5. Evaluating the Characteristics of the Product

The parameters to be evaluated in the products submitted to stability tests must be defined by the formulator and depend on the characteristics of the product under study and of the components used in the formulation.

5.1 Organoleptic Evaluation

The organoleptic characteristics determine the product acceptance parameters for the consumer. Generally, the evaluation is of:

- appearance;
- color;
- odor;
- flavor;
- feeling to the touch.

5.2 Physical-Chemical Evaluations

These are important to investigate alterations in formulation structure that are not always visually detectable. Such analyses can indicate stability problems among the ingredients or caused by the manufacturing process. The suggested physicalchemical analysis:

- pH value;
- volatile materials;
- water percentage;
- viscosity;
- particle size;
- centrifugation;
- density;
- granulometry;
- electrical conductivity;
- humidity;
- percentage of active substance when appropriate.

When necessary, different analytical techniques can be applied in the quantity assays of the formulation components, among them:

- tests based on humidity (many methodologies);
- spectrophotometry in the visible ultraviolet (UV-Vis) and infrared (IR) frequency ranges;

- chromatography (thin layer, gaseous, liquid and high efficiency).
- capillary electrophoresis, among others.

The aforementioned tests are suggestions and it is up to the formulator to evaluate their suitability for the product, taking into account the needs and specific characteristics of each company. Other tests not listed here can be used according to the specific conditions or to the formulator's interest.

5.3 Microbiological Evaluation

Microbiological evaluation makes it possible to verify the suitability of the choice of preserving system or whether interactions occurring among the formulation compounds can impair its efficaciousness.

The tests most commonly applied are:

- challenge test of the preserving system;
- microbial count.

CONSIDERATIONS ON PRODUCT STABILITY AND ITS SAFETY AND EFFICACY

The Stability Studies are useful as a predictive instrument of possible deviations from the efficiency and safety determined for the product during its development. In order to monitor the maintenance of these characteristics it is important to consider the following aspects:

- characteristics and properties of the ingredients;
- mechanisms of ingredient degradation;
- possible incompatibilities;
- risks involved at each stage of the manufacturing process;
- knowledge of the real critical factors for each formulation.

It is recommended that the safety and efficiency studies be preceded by stability studies.

The follow-up of the product in the market can confirm the initially obtained information or identify new situations that must be investigated.

6. Conclusion

As shown in this article, together with the other 2 articles in this series, Anvisa recommends that this roadmap of stability be followed in order to ensure the quality of the product to be made available in the Brazilian market.

However, it is important to remember that each company is responsible for designing the studies of its own analysis, and may add or withdraw tests, as long as the strategy to be used is justified in order to convince the regulatory agency of the model adopted.

7. Reference

1. BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Guia de Estabilidade para Produtos Cosméticos, publicada em http://portal.anvisa.gov.br/ em maio de 2004.
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□ Profile

Priscilla Viana Palhano Lima was Manager of Regulatory Affairs and Special Projects of the Brazilian public laboratory. He was directly in charge of the legal compliance of technology transfers with foreign companies from France, Poland, the United States and South Korea. He has experience in dossier analysis and elaboration of Partnership for Productive Development projects for the Ministry of Health. She is currently a consultant in Regulatory Affairs and Project Management of Partnership Projects for Productive Development for the Ministry of Health. Priscilla is the founder of the Argo Consulting company that promotes consulting in the areas of regulatory affairs, business development, project management international partnerships and technology transfers in partnership with MM Assessoria Industrial company.