ANVISA

Theme Series

National Health Surveillance Agency

Volume 1 Maio 2004

www.anvisa.gov.br

Series Quality

1

Cosmetics

Cosmetic Products Stability Guide

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Quality in Cosmetics Series
Volume 1

National Health Surveillance Agency

Cosmetic Products Stability Guide

Preface
Cosmetics -General Management

Brasília
2005

National Health Surveillance Agency Press
SEPN 515, Edifício Omega, Bl. B, Brasília – DF, ZIP CODE : 70770-502
Interne t: www.anvisa.gov.br/ e-mail: infoanvisa@anvisa.gov.br

Cosmetics- General Management

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1st edition – 2005

ISBN – 85-88233-15-0

National Health Surveillance Agency

Edition
Social and Institutional Communication Assistance Nucleus

Graphic Design
Multimedia Communication Office

Printing
Prol Gráfica

Printed in Brazil

National Health Surveillance Agency
Cosmetic Products Stability Guide/National Health Surveillance – 1st edition Brasilia: ANVISA, 2005.

52p.; 20 x 27 cm – (Quality in Cosmetics Series; v. 1)

ISBN 85-88233-15-0

I. Theme series II. Cosmetics

Presentation

It is with great pleasure that we make available to health professionals in the regulated sector, to the academic community and to other interested persons, the "ANIVSA THEME SERIES". It consists of new line of editions to overcome the lack of official publications directed towards offering technical-scientific guidance to the many sectors involved in Health Surveillance and joins itself to other editorial initiatives taken within the ambit of the Ministry of Health that are aimed at making access to information on Public Health more democratic, as one of the rights of citizenship.

With no defined periodicity or restrictions as to titles, the "Theme Series" provides many technical areas of Anvisa with an appropriate channel for the consolidation and dissemination of specific subjects directed at the interested public and always taking into account the aspects of convenience, timeliness and the priority of the proposed themes.

The first series of the new editorial line, developed by the Cosmetics area approaches the theme of Quality. This first volume of the series introduces a Cosmetic Products Stability Guide.

In the hopes that this publication may be of significant importance for the professionals and users of the National Health Surveillance System, we make ourselves available to receive comments and suggestions for the coming editions of "Anvisa Theme Series".

The Editor

Preface

In consonance with its values – Knowledge, Transparency and Cooperation – and for the accomplishment of its mission, Anvisa is now launching, in all its areas, an important line of publications: the Theme Series.

The first volume of the Theme Series – QUALITY – "Cosmetic Products Stability Guide" is an important and unpublished instrument elaborated by Anvisa professionals from the regulated sector and university professionals, during a year's work.

The main goal of this guide is the guaranteeing of quality, with emphasis on stability studies for the maintenance of the product's characteristics throughout the period of its validity. The object is to present studies and recommendations that can guide not only the professionals of the regulated sector, but also the appraisers from the governmental organs.

In publishing the present volume, Anvisa seeks to highlight the importance of Quality as one of the fundamental instruments for the protection and promotion of the population's health.

Cosmetics- General Management

Summary

1 INTRODUCTION

With the goal of attending the needs of the market and protecting the population's health, the National Health Surveillance Agency through its Cosmetics General Management division, has coordinated a special working group made up of technicians from the General Management itself, from the Public Health Lab General Management division, and of representatives of the academic community, of the productive sector and professionals of the area, for the elaboration of the present guide, which aims to offer subsidies and guidelines for the carrying out of stability studies on cosmetic products.

According to the definition established by the current legislation, Cosmetics, Personal Hygiene Products and Perfumes "are preparations composed of natural or synthetic substances for external use on the many parts of the human body, skin, capillary system, nails, lips, external genital organs, teeth and mucous membrane of the oral cavity, with the exclusive or main objective of cleaning, perfuming, changing the appearance and or correcting corporal odor and or protecting or keeping them in good condition".

In order to facilitate the reading of this guide, the expression "personal hygiene products, cosmetic and perfumes" will be substituted by the expression "cosmetic products" comprehending all the previously designated classes.

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.

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.

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 OBJECTIVE

The goal of this Guide is to present a rational approach and recommendations for cosmetic products stability evaluation, emphasizing the importance of such studies which are initiated at the development stage and should accompany the product at least until the end of its estimated period of validity.

3 GENERAL CONSIDERATIONS ON STABILITY

Stability studies on cosmetic products supply information that indicates the relative stability level of a product under the various conditions that it can be subjected to from the moment it is manufactured until the end of its validity.

This stability is relative as it varies with time and in response factors that accelerate or retard alterations in the parameters of the product. Modification within established limits do not necessarily constitute a reason for withdrawing approval of the product.

The study of cosmetic products stability contributes towards:

- Guiding the development of the formulation and of adequate containing material;
- Supplying subsidies for formulation improvement;
- Estimating the validity term and supplying information to confirm it;
- Assisting in the monitoring of organoleptic, physical-chemical and microbiological stability, by producing information about the trustworthiness and safety of products.

3.1 FACTORS THAT INFLUENCE STABILITY

Each component, active or not, can affect the stability of a product. Variables related to the formulation, to the fabrication process, to the containing material and the environmental conditions as well as transportation can influence stability. According to their origin, the alterations can be classified as extrinsic, when determined by external factors; or intrinsic, when determined by inherent formulation factors.

3.1.1 EXTRINSIC FACTORS

These are related to external factors to which the product is exposed, such as:

a) Time

The drawing near of the expiry date of the product can lead to alterations in the organoleptic, physical-chemical, microbiological and toxicological characteristics.

b) Temperature

High temperatures accelerate physical-chemical and chemical reactions, generating alterations in: component activity, viscosity, appearance, color and odor of the product.

Low temperatures accelerate possible physical reactions such as turbidity, precipitation and crystallization.

Problems created by high or very low temperatures can also derive from non-conformity during the manufacturing process, storage or transport of the product.

c) Light and Oxygen

Ultraviolet light along with the oxygen leads to the formation of free radicals and sets in motion oxidation-reduction reactions.

Products that are sensitive to light action must be conditioned away from light, in opaque or dark flasks and must also have antioxidant substances added to the formulation for the purpose of retarding the oxidation processes.

d) Humidity

This factor affects mainly the solid cosmetic forms, such as powder, bar soap, eye shadow, bath salts, among others.

Some alterations may occur in the physical appearance of the product, making

them soft or sticky or modifying weight or volume as well as leading to microbiological contamination.

e) Containing Material

The materials used for the containing cosmetic products, such as glass, metal and plastic, can influence their stability.

Suitability tests must be carried out between the containing material and the formulation, with the view to determining the best relation between them.

f) Microorganisms

The cosmetic products most susceptible to contamination are those which present water in the formulation, such as emulsions, gels, suspensions and solutions.

The adequate and validated use of additive substances (Challenge Test of the additive system) as well as the accomplishment of the Good Manufacturing Practice are necessary for the adequate conservation of the formulation.

g) Vibration

Vibration during transportation may affect the stability of the formulations, causing a division of the phases of emulsions, solidification of suspensions, alteration of viscosity, among others.

A factor which aggravates the vibration factor is the alteration of temperatures during the transportation of the product.

3.1.2 INTRINSIC FACTORS

These are factors related to nature of the formulations themselves and above all to the interaction of the ingredients among themselves or with the containing material. They result in physical or chemical incompatibilities which may, or may not be apparent to the consumer.

- **Physical incompatibility**

Alterations occur in the formulation's physical appearance, visible as: precipitation, phase separation, crystallization, formation of cracks, among others.

- **Chemical incompatibility**

a) pH

Three different aspects related to pH values must be compatible: stability of the formulation ingredients, effectiveness and safety of the product.

b) Reactions of oxidation-reduction

Oxidation or reduction processes occur leading to alterations in the activity of the active components and in the organoleptic and physical characteristics of the formulations.

c) Hydrolysis reactions

These occur through interaction with water. Esters and Amines are more susceptible to them. The higher the percentage of water in the formulation, the more likely the occurrence of this kind of reaction becomes.

d) Interactions among formulation ingredients

Undesirable chemical reactions that can occur among the ingredients of the formulation, annulling or altering its activity.

e) Interaction between formulation ingredients and the containing material

Chemical alterations that can result in alterations at the physical or chemical level to the containing material components and the ingredients of the formulation.

3.2 ASPECTS TO BE CONSIDERED IN RELATION TO STABILITY

- **Physical:** the original physical properties must be conserved, such as appearance, color, odor and uniformity, among others;
- **Chemical:** properties such as the integrity of the chemical structure, the percentages of the ingredients and other parameters must be maintained within specified limits;
- **Microbiological:** microbiological characteristics must be maintained in accordance with specifications. The accomplishment of Good Manufacturing Practices and the preservative systems used in the formulation can guarantee these characteristics.

Aside from these appearances, it is also necessary to consider the maintenance of the product's characteristics in the questions of:

- **Functionality:** the attributes of the products must be maintained unaltered in relation to the effects originally proposed.
- **Safety:** significant alterations must not occur that may influence the safety of product use.

3.3 WHEN CAN STABILITY TESTS BE DONE?

- During the development of new formulations and of laboratory and factory pilot-batches.
- When significant changes occur in the manufacturing process.
- To validate new equipment or production processes.
- When significant changes occur in the raw material being used.
- When significant changes occur in the containing material that comes into direct contact with the product.

3.4 THE FUNDAMENTALS OF STABILITY TESTING

The tests must be conducted under conditions that allow them to supply information on the stability of the product in the least time possible. For this, samples must be stored in conditions that accelerate the changes that may occur during the validity term. Care must be taken that the conditions are not so extreme that instead of merely accelerating the aging process, they provoke alterations that would not occur under market conditions. The suggested study sequence (preliminary, accelerated and “on shelf”) has the aim of evaluating the formulation by steps, looking for signs that could lead to conclusions on stability.

3.5 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.

3.6 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.

3.7 STABILITY EVALUATION PARAMETERS

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, the evaluation is:

- **Organoleptic parameters:** appearance, color, odor and flavor, whenever applicable;
- **Physical-chemical parameters:** pH value, viscosity, density, and in some cases, the monitoring of formulation ingredients;
- **Microbiological parameters:** microbial count and challenge test of the preserving system.

4 STABILITY STUDIES

Before initiating the stability studies it is recommended that the product be submitted to a centrifugation test. It is suggested that a sample be centrifuged at 3,000 rpm for 30 minutes. The product must remain stable and any sign of instability shows the need for reformulation. If approved in this test, the product can then be submitted to the stability tests.

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.

4.1.1 GENERAL CONSIDERATIONS

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.

4.1.2 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 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 we-

eks.

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.

4.3.1 GENERAL CONSIDERATIONS

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.

4.3.2 PROCEDURE

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 commu-

nication, 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 physical-chemical 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 STATISTICAL ANALYSIS

AStatistical analysis can be one of the tools used in the interpreting of data obtained during the stability studies, for the diverse aspects evaluated and at the different stages of testing.

It is necessary to adequately delineate the test, defining the variables that will be controlled and that influence the results, ex: cycles, time and temperature. Besides the factors related to studies there are other variables that are not controlled and that can influence the result. It is important to take these variables into account making sure that their influences do not affect information obtained in relation to the factors of real interest.

The data obtained in a specific stability study can be qualitative and quantitative, remembering that previous information and the histories of other products can assist in interpreting it.

The various statistical tools available must be carefully selected for use in the analysis and in the interpretation of data according to the stage of the study (selection of the formulations, accelerated stability, normal, shelf and process validation).

As examples:

- significance evaluation of the difference between two data series: hypothesis test – T test;
- determination of the capacity of a sample result and estimating real value: Estimation by trust gaps;
- tolerance limits determination of the specific characteristics: tolerance limits;
- incorporation of previous information in future event predictability: Bayes Theorem;
- evaluation of the relations between two or more variables through an equation to estimate a result: Linear regression.

It is also relevant to consider that, although there are several statistical tools and softwares that facilitate the analysis of the results, the experience and knowledge of the formulator are fundamental in the correct interpretation of the data. On many occasions statistically significant results may not be analytically relevant. On the other hand, there is the inverse situation, in which results, statistically non-significant, can be very relevant from the analytical viewpoint and should not be disregarded.

7 APPROVAL CRITERIA FOR PRODUCT STABILITY

The interpretation of the data obtained during the Stability Test depends on criteria established in accordance with the formulator's experience. The samples are evaluated in comparison with the standard sample and with products that are considered as "references" submitted to the same test conditions. Generally limits of acceptance are defined for the evaluated parameters, and the standard sample must remain unchanged during the whole life cycle of the product.

The correspondence between the data and its interpretation must be relative as in practice, the objectives and the characteristics of each product or category are quite distinct.

Generally the following criteria are considered:

- **appearance:** the product must keep itself entire during the whole of the test, maintaining it's initial appearance under all the conditions except high temperatures, freezer conditions or cycles in which small alterations are acceptable.
- **color and odor:** must remain stable for at least 15 days when exposed to sunlight. Small alterations are acceptable at high temperatures.
- **viscosity:** the limits of acceptability must be defined by the formulator, considering the visual and sensorial perceptions caused by alterations. The possibility of the consumer's also noticing them must be considered.
- **compatibility with the containing material:** the integrity of the package and the formulation must be considered, evaluating the weight, the sealing and the functionality.

In cases where the monitoring of the active ingredient percentage is necessary, the quality and performance parameters of the product must be considered.

Other parameters can be established according to the formulator and the products' specifications.

8 EXPIRY DATE OF THE COSMETIC

In Brazil, the obligatoriness of the indication of the expiry date on the packaging of cosmetic products where it can be seen by the consumer, is established in specific legislation, Resolution 79/00 and its updates and Law 8.078/90 – Consumer Protection and Defense Code.

The expiry date – characterized as the life span, in which the product maintains the original characteristics – rather than being a mere legal requirement, is, above all, a technical quality requirement as a product that is unstable from the physical-chemical, microbiological or toxicological point of view not only loses effectiveness but can also cause damage and impair consumer confidence.

Due to the peculiar nature of the formulations of cosmetic products, it is accepted as a general rule that it is impossible to elect one isolated ingredient separated from the rest of the formulation. Thus it is difficult to apply the relation between kinetic constant, temperature and a direct correlation of these variables with the estimated expiry date. However, the expiry date can be estimated by means of the Stability Studies and it must be confirmed using the shelf test.

9 CONCLUSION REPORT ON STABILITY STUDIES

At the end of the Stability Studies, the elaboration of a report with the following information is suggested:

- Identification of the product
- Containing material used in the test
- Study conditions (sample storage conditions, test time period and periodicity of the evaluations)
- Results (can be registered in a chart, relating the storage conditions, time and periodicity of the analysis)
- Conclusion (evaluate the obtained results, report if the product was approved or not, conditions that the test was conducted and estimate the expiry period)
- The signature of the person responsible for the study

10 APPENDICES

APPENDIX I – TESTS AND METHODOLOGIES

1 ORGANOLEPTIC TESTS

Parameters are offered that make it possible to evaluate, immediately, the state of the study sample, using comparative analysis, with the aim of verifying alterations such as: phase separation, precipitation and turbidity, allowing the primary recognition of the product. A reference sample must be used, recently elaborated, or a sample of the product, stored at an adequate temperature, in order to avoid changes in the organoleptic properties.

1.1 APPEARANCE

The sample characteristics are visually observed, verifying if there were any macroscopical modifications in comparison with the standard established.

The appearance can be described as: granular, dry dust, moist dust, crystalline, paste, gel, fluid, viscous, volatile, homogeneous, heterogeneous, transparent, opaque, milky, etc

The sample can be classified according to the following criteria:

- **normal, without alteration;**
- **slightly separated, slightly precipitated or slightly turbid;**
- **separated, precipitated or turbid.**

1.2 COLOR

The methods used to verify color are many; the most used being the visual and spectrophotometric methods.

Visual

The color of the sample is compared with the established standard in a flask with the same specification. The used light sources can be white, natural or in special chambers with many types of light sources.

The sample of the product can be classified according to the following terms:

- **normal, without alteration;**
- **slightly modified;**
- **modified;**
- **intensively modified.**

Spectrophotometric

The sample of the product under study, either pure or in solution is submitted to scanning analysis by spectrophotometry in the visible light band and its spectrum is compared to the reference spectrum. Variations in the intensity of the band (hyperchromic and hypochromic) indicate alterations in the intensity of the color or even modification of the coloring material.

1.3 ODOR

The odor of the sample is compared with the established pattern directly, by smelling it.

The sample can be classified according the following criteria:

– **normal, without alteration;**

– **slightly modified;**

– **modified;**

– **intensively modified.**

1.4 FLAVOR

The flavor of the sample is compared with the established standard, directly by tasting it.

The sample can be classified according to the following criteria:

– **normal, without alteration;**

– **slightly modified;**

– **modified;**

– **intensively modified.**

2 PHYSICAL-CHEMICAL TESTS

The physical-chemical evaluations allow the formulator to detect future problems that can affect the stability and the quality of the product.

2.1 HYDROGEN ION POTENTIAL - pH

The methods used for the verification of the pH value of the samples are:

- **colorimetric calibration:** using universal indicators, and prepared ranges of buffer solutions and indicators. Presents low sensitivity. Small variations in acidity or alkalinity in the formulations are hardly observeable.
- **potentiometric calibration:** a pH meter is used (pedometer) and the value is measured by the potential difference found between two electrodes immersed in the study sample. It is important to use an electrode suitable for the type of formulation being analyzed.

Both methods above lead to numerical results easily interpreted.

2.2 VOLATILE MATERIALS

A measured quantity of the sample, analytically weighed, is submitted to drying in an oven heated to 105°C until it attains a constant weight.

The difference in the mass of the sample before and after the test shows the quantity of the mass of the formulation that will be volatilized under such conditions and this is usually expressed as a percentage. This method offers numerical results, easily interpreted.

2.3 WATER CONTENT

Many methods are used for the quantitative determination of water in a finished product, the most common being: Gravimetric Method, Distillation Method in Dean & Stark apparatus and the Karl-Fischer Titration Method. These methods produce numerical results, easily interpreted.

2.4 VISCOSITY

Viscosity is a variable that characterizes a system in its rheological aspect. The evaluation of this parameter helps to determine if a product presents the appropriate consistency or fluidity and can indicate if stability is adequate and thus gives an indication of the product's behavior over a period of time.

The most frequent methods used in determining the viscosity of a fluid use, viscosimeters of the capillary or rotating type or with orifices. Such methods supply numerical results, easily interpreted.

2.5 ANALYSIS OF PARTICLE DISTRIBUTION BY SIZE

The analysis of the profile of the particle distribution curve, during the stability period, makes it possible to accompany the microscopic behavior of the particles in suspension, highlighting instability phenomena.

Different factors both in the formulation itself and in the manufacturing process, affect particle formation and consequently particle dimensions, notably the following: the preparation method, the quantity of mechanical energy introduced in the system, the viscosity differences among the phases and the type and quantity of emulsifier used.

Most of the equipments used for this analysis are based on the principle of disper-

sion or diffraction of laser light. The laser beam goes through the cell that contains the sample, and the particles disperse the light in beams that depend on: the wavelength, the optical properties of the sample and the particle dimension. After the analysis, the results, with the dimensions of the particles detected are extrapolated to apply to the entire population of particles in the sample.

The method offers numerical results, easily interpreted, in which the concentration, dimension and particle shapes can be evaluated.

2.6 CENTRIFUGING

The force of gravity acts on the sample making the particles move within it.

The centrifuging test produces stress in the sample, simulating an increase in the force of gravity and increasing the mobility of the particles thus anticipating possible instabilities. These changes may appear in the form of precipitation, separation of phases, caking, or coalescence among others.

The sample is centrifuged at a standardized temperature, time and speed. Afterwards, the sample is visually evaluated.

2.7 DENSITY

This is the ratio between the mass of a substance and the volume that it occupies, and generally for the liquids, it is determined using the pycnometer or the densimeter. In the case of liquids or semi-solids this parameter can indicate the incorporation of air or the loss of volatile ingredients.

For determining the (apparent) density of powders, a test tube and a balance are used. The apparent density is related to the capacity of the recipient.

It is important to avoid overflow or an apparent lack of product in the recipient that holds it, because the declared weight may be within the specified limits, but the consumer will have the impression that some of the product is missing.

2.8 GRANULOMETRY

In the product there are particles/drops of varying diameters. The proportion of particles outside the specified limits can influence in the appearance, in the performance and in the color of the product. For this kind of test, the following methods can be used:

- **sifting:** silk screen sifters are used with standardized mesh, to specify the size of the particles;
- **laser diffraction:** used to evaluate very small-sized particles.

2.9 ELECTRICAL CONDUCTIVITY

Uses measurement of the passage of electric current through the medium being evaluated using conductivity meters. The alteration of the electrical conductivity of disperse systems can indicate instabilities. An increase in conductivity may be related to coalescence and a decrease to aggregation.

2.10 SPECTRUM PHOTOMETRY

Ultraviolet/Visible (UV/Vis): the absorption of light by a substance in the ultraviolet/visible range of the spectrum depends on the electronic structure of the molecule. Through the incidence of light energy on the sample, a spectrum is obtained that is used to obtain a graph plotting absorption/transmission against wavelength or frequency. The height (intensity) of the peaks (spikes) on the plotted line may be altered by changes in the concentration of the substance. This analysis can be used for identifying and dosing substances.

Infrared (IR): spectrum-photometry in the infrared (IR) frequencies is a technique widely used for identifying compounds as it is a method that is both fast and sensitive. It permits the identification of the substance by comparing its absorption bands with those of standardized chemicals. In contrast with the few spikes that can be observed in the UV/Vis range, the spectrum in the infrared frequencies offers many absorption bands generating a set of information about the chemical structure of the analyzed substance.

2.11 CHROMATOGRAPHY

Chromatographic methods are used to identify and quantify the ingredients. The evaluation of a formulation component, over many time intervals, reveals its stability profile under the specified conditions. The following methods can be mentioned: Slender Layer Chromatography (SLC), Liquid and High Efficiency Chromatography (LHEC) and Gas Chromatography (GC).

3 MICROBIOLOGICAL TESTS APPLIED TO STABILITY STUDIES

The cosmetic products must be produced, stored, transported and distributed in a safe way, and must comply with Resolution 481/99. The presence of water and organic components in the formulation favors the growth of microorganisms. In some cases, this affects the structure of the additive agents, influencing the stability of the product and this justifies a microbiological evaluation of the product.

With the development of Good Manufacturing Practices, it is understood that the microbiological quality of a cosmetic must not depend exclusively on the system of preservatives. However, as their use is indispensable, the choice of the additives must be adequate in order to be effective. Besides, it must be considered that the additives may be partially or totally inoperative thus leaving the product without the hoped for protection. Therefore, effectiveness tests for the additives must be an essential part of the safety data of the cosmetic products. These tests are aimed at determining the type of additive and the minimum effective concentration necessary to assure satisfactory protection of the product from the moment of manufacture until its final use by the consumer.

3.1 CHALLENGE TEST OF THE PRESERVATIVE SYSTEM

The challenge test of the additive or preservative system consists in purposely contaminating the product with specific microorganisms and evaluating the sample at defined time intervals with the objective of evaluating the effectiveness of the preservative system necessary to the protection of the product.

The used of additives must be in conformity with that established in Resolution 162/01 and its updated versions.

For a wider approach, the test must be done in at least two phases: the first after the definition of the formula of the product; and the second, after the end of the stability testing and/or the test for formulation compatibility with the containing material.

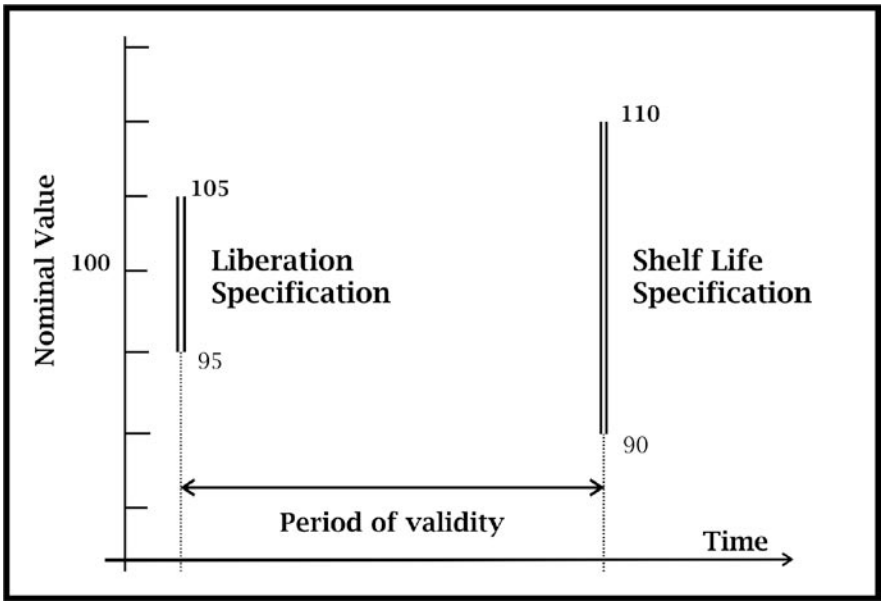
The analysis methods are described in the official compendium and orientation guides for cosmetic microbiological analysis and effectiveness tests of additive systems(Pharmacopeias, ABC Microbiology Guide, Guideline of CTFA, among others).

If, at the moment of manufacture, a batch presents specifications close to the established limits for the product, then certainly a slight change may lead to the transgression of these limits and the occurrence of non-conformity that can reduce the time that the product maintains itself suitable for using.

With the aim of maintaining the expiry date projected for the product, it is desirable that two specifications be established: one denominated "Liberation Specification" to be adopted an the moment of manufacture, and the other denominated "Shelf Life Specification", which characterizes the product over the period of its useful life.

During the time the product is being stored under market conditions, its specifications can vary within the limits established by the liberation Specifications and the Shelf Life Specifications, and this is especially true for those parameters for which the product has lower stability.

Figure 1 exemplifies the possibility of establishing, a variation range of ± 5% of the nominal value of a certain parameter as a liberation Specification; and a variation range of ± 10% as a Shelf Life Specification.



Picture 1: Liberation specification versus Shelf Life specification (IFSCC Monograph, 1992).

APPENDIX III – BRAZILIAN LEGISLATION

Stability studies are aimed at evaluating the capacity of a product maintain the same organoleptic, physical-chemical, microbiological characteristics as well as its safety and effectiveness. Thus the stability study must be seen as a necessary requirement for the product's quality guarantee and not merely as a requirement of the regulatory agency.

In Brazil, it's responsibility of the National Health Surveillance Agency – Anvisa/ MS to regulate, inspect and control the production and the commercialization of cosmetic products, in order to offer safe products and with quality, on the market; contributing in this way towards the protection of the population's health.

The regulatory requirements on stability of cosmetic products are founded on the following normative acts:

- **Resolution 79/2000** – rules and procedures for the registering of personal hygienic products, cosmetics and perfumes and lists of permitted coloring substances and of substances whose use is restricted.
- **Resolution 335/1999** – rules and procedures for the notification of risk level 1 products - Article 2: "the manufacturer or importer must have verified data that attests the quality, safety and effectiveness of the products ".
- **Regulation 348/1997** – Good Manufacturing Practices Guide and inspection routines. Item 12.15: "stability studies of the products with records made of test conditions, results and methods of analysis adopted".
- **Resolution 481/1999** – Parameters for Microbiological Control of cosmetic products.
- **Resolution RDC 161/2001** – List of approved ultraviolet light filters.
- **Resolution RDC 162/2001** – List of approved additives.
- **Technical Reports of the Cosmetics Technical Chamber** – technical recommendations with specific requirements for certain types of products or substances.

11 GLOSSARY

Additives: substances added to personal hygienic products, cosmetics and perfumes with the primary purpose of preserving them from damages or deterioration caused by microorganisms during their manufacture and storage, as well as protecting the consumer from unadvertised contamination during the use of the product.

Antioxidant: agent that retards the deterioration by oxidation of substances that are susceptible to the action of oxygen action, such as: oils, greases, vitamins, essences and coloring substances. Acts directly on the substances or on the environment.

Coalescence: phenomenon in which two or more drops of the internal phase of a disperse system come together with rupture of the interfacial film, combining to forming a bigger drop. It's an irreversible process.

Compatibility: characteristic that indicates the possibility of eventual interactions between the formulation and the containing material, determining whether the attributes of the products will be kept within the initial specification and without impairment of the product's performance.

Efficacy: quality or property whereby the desired effect is achieved whether the evaluation be of a part (sample) or of the whole.

Functionality: refers to the attributes of the product (in the formulation or in the package) that must be kept without alteration and are related to the proposed purpose of the product.

Ingredient/component: chemical substance used in the elaboration of cosmetic products.

Linear regression: analysis of sample data that evaluates the interference relation of one variable on another, considering the set of data as a whole.

Lot/Batch: determined quantity of a product obtained from a continuous production line and made up of products having the same specifications.

Official Methodology: described methodology in the official orientation compendium such as the Pharmacopeias and Official Forms.

Organoleptic characteristics: substance and product characteristics that refer to their sensorial profile identified by: appearance, color, odor and flavor.

Oxidation: designates the transference of electrons between two substances. Depends on the presence of oxygen and is accelerated by the presence of light and of a catalyzer.

Oxidation-reduction Reaction: involves the transference of electrons or the alteration of the oxidation number of the involved substances.

Photo-stability (window test): test that evaluates the stability of a product exposed to light radiation, the source of which may be direct sunlight or artificial lamps.

Pilot-lot: production of an initial quantity, with the objective of validating the developed product and the efficiency of the manufacturing process.

Procedure: instructions in which the purpose is to document and orient the steps of a process related to a certain operation.

Reference Sample, Reference Standard or Standard: products or substances that have ideal characteristics and testify conformity, serving as adequate parameters for quality comparisons.

Oxidação: designa a transferência de elétrons entre duas substâncias. Depende da presença de oxigênio e é acelerada pela presença da luz e de um catalisador.

The denomination "standard" also involves chemical reference substances and standard biological substances that are used in the products' specifications for evaluating the chemical and biological quality of the active ingredients and of the finished products.

Relative Humidity (RH): ratio between the water vapor pressure in the atmosphere and saturated vapor pressure at the same temperature.

4 climatic zones are considered (I to IV) differentiated by the characteristics of the prevailing environmental conditions. In this classification, Brazil is considered as belonging Zone IV, hot climate (tropical) or Global Market. According to this classification, the value of the relative humidity for stability studies is taken to be 65± 5% RH.

Rheology: study of the flow and deformation properties of materials under the influence of external forces. It comprises elasticity, viscosity and plasticity.

Sensorial Analysis: study that evaluates the aspects that can be perceived by the sense organs.

Shipping test: test that evaluates the stability of a product facing different variables during transportation: temperature, vibration, impact, pressure and humidity. Can be done in a real or simulated form.

Specification: description of attributes of the material, substance or product that are required by the norms or established by the company, so as to ensure the quality during the manufacture and use.

Standardization: norm that is destined to restrict the variables of a process by the establishment of a methodical and precise set of conditions to be fulfilled.

Syneresis: spontaneous separation of a homogeneous colloidal system into two phases (gel and liquid).

Synergism: physical-chemical or biochemical interactions in which the effect obtained by the combined action of two different substances is greater than the sum of the individual effects.

Thermal Stress: condition in which the product is submitted, occasionally or intentionally, to significant temperature changes, whereby it may suffer alterations.

Viscosity: is a measure of the resistance to flow in a liquid when one layer is moving in relation to another.

Water activity (Wa): measurement that represents the extent to which the water is linked to the product's ingredients, being available to a variable extent to participate in chemical, and biochemical reactions the proliferation of microorganisms.

Zero Time: moment in which the first recording of an analyzed parameter is made. Can be established immediately after manufacture or after a specific time (for example: 24 hours).

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Special thanks go to the special Working Group of the Cosmetology Association responsible for the initial proposal that gave rise to guide, and to those who collaborated in revising the work:

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Brasília, 2005.

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