HEALTH DEPARTMENT

Official Mexican Standard NOM-073-SSA1-2005, Stability of Drugs and Medicine (modifies the NOM-073-SSA1-1993, Stability of Medicine, published on August 3, 1996)

On the margin, a seal bearing the national symbol and the words "United Mexican States – Health Department.

OFFICIAL MEXICAN STANDARD NOM-073-SSA1-2005,
STABILITY OF DRUGS AND MEDICINE
(MODIFIES NOM-073-SSA1-1993, STABILITY OF MEDICINE, PUBLISHED ON AUGUST 3, 1996)

ERNESTO ENRIQUEZ RUBIO, President of the National Advisory Committee on the Standardization of Sanitary Regulation and Development, pursuant to Article 39 of the Federal Public Administration Organic Law; Article 4 of the Federal Law on Administrative Procedures; Article 3, fraction XXIV, Article 13, Section A, fraction I; Article 17 bis, 194, 194 bis, 195,197,201,210 to 214, 257 to 261 and others applicable from the General Health Law; Article 3 fraction XI, article 38 fraction II, article 40 fractions I, V, XI and XII; 41, 43, 47 and 52, of the Federal Law on Metrology and Normalization; Articles 9, 10, 11, 15, 100, 102, 109, 111 of the Health Input Regulation; Articles 28 and 39 of the Federal Law Regulation on Metrology and Normalization; Article 2 Section C, fraction II and Article 34 of the Internal Regulations of the Health Department and Article 3 fraction I and II of the Federal Commission Regulation for the Protection against Sanitary Risks, I take the liberty to order the publishing, in the Official Gazette of the Federation, of the Official Mexican Standard NOM-073-SSA1-2005, Stability of Drugs and Medicine (Modifies the NOM-073-SSA1-1993, Stability of Medicine, published on August 3, 1996)

W H E R E A S

That on November 27, 2002, in compliance with that foreseen in article 46, fraction I of the Federal Law on Metrology and Normalization, the Head Office of Medications and Health Technologies presented before the National Advisory Committee for the Standardization of the Sanitary Regulation and Development, the pre-project of the present Official Mexican Norm.

That on the August 20, 2003, in compliance with the agreement of the Committee and that foreseen in article 47, fraction 1 of the Federal Law on Metrology and Normalization, the project of the present Official Mexican Norm was published in the Official Gazette of the Federation, the project of the present Official Mexican Norm, in order that, during the following sixty calendar days after the said publication, the interested parties will present their comments to the National Advisory Committee for the Standardization of the Sanitary Regulation and Development.

That, dated previously, published in the Official Gazette of the Federation, the answers to the comments were received by the above-mentioned Committee, under the terms of article 47, paragraph III of the Federal Law on Metrology and Normalization.

That in virtue of the above considerations and having the approval of the National Advisory Committee for Standardization of Sanitary Regulation and Development, the following Standard is issued:

OFFICIAL MEXICAN STANDARD NOM-073-SSA1-2005,
STABILITY OF DRUGS AND MEDICINE
(MODIFIES NOM-073-SSA1-1993, STABILITY OF MEDICINE, PUBLISHED ON AUGUST 3, 1996)

P R E F A C E

The following organisms and institutions participated in the elaboration of the present Official Mexican Standard:

THE HEALTH DEPARTMENT - General Management on Juridical Affairs
FEDERAL COMMISSION FOR PROTECTION AGAINST SANITARY RISKS.
Sanitary Authorization Committee
Commission on Evidence and the Handling of Risks.
Commission on Analytical Control and Coverage Extension
THE MEXICAN SOCIAL SECURITY INSTITUTE
THE SAFETY AND SOCIAL SERVICES INSTITUTE FOR STATE WORKERS.
THE NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO
The Chemistry Faculty
NATIONAL POLYTECHNIC INSTITUTE
National School on Biological Science
Higher National School of Medicine
Advanced Studies and Research Centre
NATIONAL CHAMBER OF THE PHARMACEUTICAL INDUSTRY.
NATIONAL CHAMBER OF THE TRANSFORMATION INDUSTRY. Section 89
COLEGIO NACIONAL DE QUIMICOS FARMACEUTICOS BIOLOGOS, MEXICO, A.C.
INTERINSTITUTIONAL COMMISSION ON GOOD MANUFACTURING PRACTICES
ASOCIACIÓN FARMACEUTICA MEXICANA, A.C.
ASOCIACIÓN MEXICANA DE LABORATORIOS FARMACEUTICOS, A.S.
NATIONAL ACADEMY OF PHARMACEUTICAL SCIENCE
CENTRO A.F. DE ESTUDIOS TECNOLOGICOS, S.A.
BAYER DE MEXICO, S.A. DE C.V.
GRUPO ROCHE SYNTEX DE MEXICO, S.A. DE C.V.
LABORATORIOS KENER, S.A. DE C.V.
LABORATORIOS PISA, S.A. DE C.V.
LABORATORIOS SILANES, S.A. DE C.V.
MERCK SHARP AND DOME DE MEXICO, S.A. DE C.V.
SANOFI-SYNTHELABO DE MEXICO, S.A. DE C.V.
NOVARTIS FARMACEUTICA, S.A. DE C.V.

I N D E X

0 Introduction

This Official Mexican Standard is issued in order to establish the requirements of the stability studies that should be performed to the drugs and medications commercialized in Mexico

1 Objective

The purpose of the stability studies is to provide documented evidence of how the quality of a drug or medication varies with time, because of environmental factors such as temperature, humidity and light. The studies allow to determine the appropriate storage conditions, retest period and shelf-life.

2 Scope

This Official Mexican Standard is to be observed within the national territory for: Manufacturing plants or Laboratories of Raw Materials for the elaboration of medicines or biological products for Human consumption and Manufacturing Plants or Laboratories of Medications or Biological Products for Human Consumption.

3 References

3.1 Official Mexican Standard NOM-008-SCFI-1993, General System of Measuring Units

3.2 Official Mexican Standard NOM-072-SSA1-1993 Labelling of medications

3.3 Official Mexican Standard NOM-059-SSA1-1993, Good Manufacturing Practices for establishments of the chemical-pharmaceutical industry dedicated to the manufacturing medications.

3.4 Official Mexican Standard NOM-164-SSA1-1998, Good Manufacturing Practices of drugs

4 Definitions, symbols and abbreviations

For this standard, the following is understood:

4.1 Definitions

4.1.1 **Quality of a drug or medications**. Compliance of established specifications that guarantee the identity, purity, strength and any other chemical, physical or biological characteristic ensuring its usage capability.

4.1.2 **Storage conditions.** The ones indicated in the label of the drug or medication

4.1.3 **Complete analysis designs.** A stability study design that includes the analysis of all parameters, to all conditions established in the protocol

4.1.4 **Design of reduced analysis**

4.1.4.1 **Design per category.** Design of a stability study in which only the samples of the extremes of certain design factors (as concentration of the drug, container size, closure, amount of units) are analyzed in all times established in a complete design. It is assumed that the stability of the medication in the intermediate design factor is represented by the extremes of the same.

4.1.4.2 **Fractionated factorial design.** The design of a stability study where only a selected group of samples from the total number of samples is analyzed to a specified sampling point. In the subsequent sampling points, other groups of samples are selected and the analysis of the same is carried out. It is assumed that the stability of the analyzed samples represents the stability of all the samples to a specific sampling point.

4.1.5 **Primary package.** Elements of the container-closure, which are in contact with the drug or medication.

4.1.6 **Secondary package.** The elements of the package in which the drug or medication is sold and not in direct contact with them.

4.1.7 **Stability specifications.** Physical, chemical, biological or microbiological requirements that determine that a drug or medication should comply with through their shelflife.

4.1.8 **Release specifications.** Physical, chemical, biological or microbiological requirements that determine that a drug or medication is adequate for its release.

4.1.9 **Stability**. Is the capacity of a drug or medication to remain within the established specifications of quality inside its container during its shelf life.

4.1.10 **Stability studies.** Tests carried out on a drug or medication during a specific time, under the influence of temperature, humidity or light within its container.

4.1.11 **Accelerated stability studies**. Studies designed under exaggerated storage conditions to increase the chemical or biological degradation or the physical changes of a drug or medication.

4.1.12 **Long term stability studies**. Studies designed under controlled storage conditions to evaluate the physical, chemical, physicochemical, biological or microbiological properties of a medicine during the retest period or shelf-life, respectively.

4.1.13 **Annual stability program.** Studies designed to verify the stability of a drug or medication from the production lots, under long-term stability conditions.

4.1.14 **Drug.** Any natural or synthetic substance that is pharmacologically active, can be identified by its physical or chemical properties or biological activity, is not in pharmaceutical form, and may be used as a medicine or an ingredient in a medicine

4.1.15 **Known drug.** The drug being previously used in the country

4.1.16 **New drug.** The drug that has not being previously used in the country

4.1.17 **Expiry date:** Date that indicates the end of the shelf-life of the medication.

4.1.18 **Re-test date:** Date in which a drug or additive is analyzed to ensure that it continues to be adequate for its use.

4.1.19 **Pharmaceutical form.** It is the mixture of one or more drugs with or without additives, that allows its administration.

4.1.20 **Lot.** The amount of a drug or medication produced in a manufacturing cycle and which essential characteristics is its homogeneity.

4.1.21 **Production lot**. Lot destined for the commercialization

4.1.22 **Pilot lot**. Lot elaborated by a representative procedure simulating that of the production. In the case of solid pharmaceutical forms, it shall correspond to at least 10% of the production lot or 100 000 tablets or capsules; in the case of other pharmaceutical forms a technical justification of its size shall be presented

4.1.23 **Medication**. Any substance or mixture of substances of natural or synthetic origin that has a therapeutic, preventive or rehabilitation effect, presented in a pharmaceutical form and that it may be identified as such by its pharmacological activity and its physical, chemical and biological characteristics.

4.1.24 **Known medication**. A medication that has been registered in the country

4.1.25 **New medication.** A medication that has not been registered in the country.

4.1.26 **Analytical method indicative of stability.** Quantitative analytical method for a drug or medication, capable of distinguishing each active ingredient from other substances and from is degradation products.

4.1.27 **Major change.** The one producing a significant impact on the quality and performance of the formulation. Equivalent to Level 3 of the Change Classification

4.1.28 **Minor change.** The one that does not produce a significant impact on the quality and performance of the formulation. Equivalent to Level 1 of the Change Classification

4.1.29 **Moderate change.** The one that might produce a significant impact on the quality and performance of the formulation. Equivalent to Level 2 of the Change Classification

4.1.30 **Shelf-life.** It is the time a medication inside the commercialization package and stored under the conditions indicated in its label remains within the established specifications.

4.1.31 **Tentative shelf-life.** It is the provisional shelf-life that the Health department authorizes, based on the results of the accelerated stability studies or the statistical analysis of the long-term stability data available.

4.1.32 **Stability protocol.** Study design relative to tests and acceptance criteria, lot characteristics, handling of samples, conditions of the study, analytical methods and package materials.

4.1.33 **Re-test period.** The time during which a drug or an additive remains within the established specifications, under defined storage conditions.

4.1.34 **Container closure system.** The set of packaging materials that contain and protect the pharmaceutical form. It includes both the primary and the secondary container, if the latter complies with the function of providing additional protection to the product.

4.1.35 **Validation.** Documented evidence demonstrating that through a specific process we obtain a product that consistently complies with the specifications and the quality attributes established.

4.1.36 **Shelf-life**. It is the period during which a medication remains within the established specifications, under the storage conditions indicated on the label, inside the commercialization container.

4.1.37 **Climatic Zone.** Geographical area classified by its climatic conditions prevailing during all year round. The United Mexican States are considered within the Climatic Zone II.

4.2 **Symbols and abbreviations**

±	more or less
%	percent
°C	centigrade
RH	relative humidity

5 **New drug**

5.1 Selection of lots. The stability studies should be carried out in at least three pilot lots of the drug manufactured by the same synthesis route and applying the manufacturing method that simulates the process that shall be used in the manufacture of the production lots.

5.2 Container closure system. The studies must be carried out in the same container-closure system or a representative system to the one proposed for its storage and distribution.

5.3 Parameters to be evaluated and analytical methodology. The study protocol must include the stability parameters or specifications that are susceptible of changing during the study and that may influence its quality, safety or efficacy. The tests must cover, in its case, physical, chemical, biological or microbiological parameters. Validated analytical methods indicative of stability must be applied.

5.4 Conditions of the study. The conditions of the study and its duration should be enough to cover the storage, distribution and usage of the drug apply the following charts:

5.4.1 General case:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	40°C ± 2°C / 75% ± 5% RH	6 months	0, 3 and 6 months
Intermediate stability**	30°C ± 2°C / 65% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH	12 months	0, 3, 6, 9 and 12 months

* It is the decision of the manufacturer to carry out the long-term stability studies at 25°C ± 2°C / 60% ± 5% RH or at 30°C ± 2°C / 65% ± 5% RH

** If 30°C ± 2°C / 65% ± 5% RH is the long-term stability study condition, then it is not necessary to make the study at the intermediate condition.

5.4.1.1 If the long-term stability studies are carried out at 25°C ± 2°C / 60% ± 5% RH and significant changes occur during the 6 months period of the accelerated stability stud, additional tests should be carried out at the intermediate condition and evaluate the results according to the significant changes criteria. The intermediate condition study should include all tests, unless the contrary is justified. Under this condition, at least,

data from the 0, 3, and 6 months of the study should be presented at the moment of requesting the registration of the medication, and continue the study up to 12 months.

5.4.1.2 In this case, a significant change should be understood as any non-fulfilment of the established stability specifications.

5.4.1.3 The long-term stability for a drug with a proposed retest period of at least 12 months, shall continue with an analysis frequency of every 3 months during the first year, every 6 months on the second year and annually afterwards.

5.4.2 Drugs to be stored at refrigeration condition:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	25°C ± 2°C / 60% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability	5°C ± 3°C	12 months	0, 3, 6, 9 and 12 months

When there are significant changes between the 3 and 6 months of the accelerated stability study, the proposed retest period should be based in the long-term stability data.

5.4.3 Drugs to be stored under freezing conditions:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Long-term stability	-20°C ± 5°C	12 months	0, 3, 6, 9 and 12 months

To evaluate the impact of the short excursions, outside the conditions established in the label, a pilot lot should be subjected to 5°C ± 3°C or 25°C ± 2°C during an appropriate period, as the case may be.

6 Known drug

6.1 Selection of lots. The stability studies should be carried out according to one of the two following options.

Option 1. In at least two production lots manufactured by the same synthesis route and under the study conditions indicated in paragraph 6.4, and subject a third production lot once the latter is continuous.

Option 2. Three pilot lots manufactured by the same synthesis route, under the study conditions indicated in paragraph 6.4. In this option, the three production lots should be subjected to long-term stability studies using the same protocol.

6.2 Container-closure system. The studies must be carried out in the same container-closure system or a representative system than the one proposed for its storage and distribution.

6.3 Parameters to be evaluated and analytical methodology. The study protocol must include the stability parameters or specifications that are susceptible of changing during the study and that may influence its quality, safety or efficacy. The tests must cover, in its

case, physical, chemical, biological or microbiological parameters. Validated analytical methods indicative of stability must be applied.

6.4 Conditions of the study. The conditions of the study and its duration should be enough to cover the storage, distribution and usage of the drug. Apply the following charts:

6.4.1 General case:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	40°C ± 2°C / 75% ± 5% RH	6 months	0, 3 and 6 months
Intermediate stability**	30°C ± 2°C / 65% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability*	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH	6 months (option 1) 12 months (option 2)	0, 3 and 6 months 0, 3, 6, 9 and 12 months

* It is the decision of the manufacturer to carry out the long-term stability studies at 25°C ± 2°C / 60% ± 5% RH or at 30°C ± 2°C / 65% ± 5% RH

** If 30°C ± 2°C / 65% ± 5% RH is the long-term stability study condition, then it is not necessary to make the study at the intermediate condition.

6.4.1.1 If the long-term stability studies are carried out at 25°C ± 2°C / 60% ± 5% RH and significant changes occur during the 3 months period of the accelerated stability stud, additional tests should be carried out at the intermediate condition and evaluate the results according to the significant changes criteria. The intermediate condition study should include all tests, unless the contrary is justified. Under this condition, at least, data from the 0, 3, and 6 months of the study should be presented at the moment of requesting the registration of the medication, and continue the study up to 12 months.

6.4.1.2 In this case, a significant change should be understood as any non-fulfilment of the established stability specifications.

6.4.1.3 The long-term stability for a drug with a proposed retest period of at least 12 months, shall continue with an analysis frequency of every 3 months during the first year, every 6 months on the second year and annually afterwards.

6.4.2 Drugs sensible to temperature. Apply the conditions indicated in paragraphs 5.4.2 and 5.4.3, as necessary.

7. New medication

7.1 Selection of lots. The stability studies should be carried out in at least three lots of the medication, manufactured with the same qualitative and quantitative formula and applying the manufacturing process that simulates the process that should be used in the manufacture of the production lots to be sold. Two of the three lots should be at least pilot lots. The third lot should be lesser in size. When possible, the medication lots should be manufactured using the different lots of the active ingredient.

7.2 Container-closure system. The studies must be carried out in the same container-closure system or a representative system to the one proposed for its storage and distribution.

7.3 Parameters to be evaluated and analytical methodology. The study protocol must include the stability parameters or specifications that are susceptible of changing during the

study and that may influence its quality, safety or efficacy. The tests must cover, in its case, physical, chemical, biological or microbiological parameters. Validated analytical methods indicative of stability must be applied.

7.4 Submit the data obtained in the accelerated stability studies according to that indicated in the corresponding chart, and the long-term stability data available at the moment of making the registration application.

7.5 Conditions of the study. The conditions of the study and its duration should be enough to cover the storage, distribution and usage of the drug apply the following charts:

7.5.1 General case:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	40°C ± 2°C / 75% ± 5% RH	6 months	0, 3 and 6 months
Intermediate stability**	30°C ± 2°C / 65% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability*	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH	12 months	0, 3, 6, 9 and 12 months

* It is the decision of the manufacturer to carry out the long-term stability studies at 25°C ± 2°C / 60% ± 5% RH or at 30°C ± 2°C / 65% ± 5% RH

** If 30°C ± 2°C / 65% ± 5% RH is the long-term stability study condition, then it is not necessary to make the study at the intermediate condition.

7.5.1.1 If the long-term stability studies are carried out at 25°C ± 2°C / 60% ± 5% RH and significant changes occur during the 6 months period of the accelerated stability stud, additional tests should be carried out at the intermediate condition and evaluate the results according to the significant changes criteria. The intermediate condition study should include all tests, unless the contrary is justified. Under this condition, at least, data from the 0, 3, and 6 months of the study should be presented at the moment of requesting the registration of the medication, and continue the study up to 12 months.

7.5.1.2 The following are considered significant changes during accelerated stability:

- 5 percent of variation on the initial strength, or else the non-fulfilment of the acceptance criteria for strength, when applying biological or immune methods.
- Any degradation product exceeding the specification limit
- When the pH limits are exceeded, as applicable.
- When the dissolution specification limits are exceeded for 12 dose units, as applicable.

When not complying with the specifications of appearance and physical properties.

7.5.2 Medication contained in impermeable and semi-permeable containers

7.5.2.1 For parenterals of great and small volume and liquid preparations for ophthalmic, otic and nasal application, packed in plastic bags, semi-rigid plastic containers, plastic ampoules, ampoule bottles and plastic bottles with or without dropper, which may be susceptible to the loss of humidity, follow this next chart:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	40°C ± 2°C / not more than 25% RH	6 months	0, 3 and 6 months
Intermediate stability**	30°C ± 2°C / 35% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability*	25°C ± 2°C / 40% ± 5% RH or 30°C ± 2°C / 35% ± 5% RH	12 months	0, 3, 6, 9 and 12 months

* It is the decision of the manufacturer to carry out the long-term stability studies at 25°C ± 2°C / 60% ± 5% RH or at 30°C ± 2°C / 65% ± 5% RH

** If 30°C ± 2°C / 65% ± 5% RH is the long-term stability study condition, then it is not necessary to make the study at the intermediate condition.

7.5.3 For liquids in glass jars, ampoule bottles or sealed glass ampoules, which have an impermeable barrier against water loss, follow this chart:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	40°C ± 2°C / 75% ± 5% RH	6 months	0, 3 and 6 months
Intermediate stability**	30°C ± 2°C / 65% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability*	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH	12 months	0, 3, 6, 9 and 12 months

* It is the decision of the manufacturer to carry out the long-term stability studies at 25°C ± 2°C RH / 60% ± 5% RH or at 30°C ± 2°C RH/ 65% ± 5% RH

** If 30°C ± 2°C RH / 65% ± 5% RH is the long-term stability study condition, then it is not necessary to make the study at the intermediate condition.

7.5.3.1 In the event there is a loss of water of more than 5% from the initial value, during the three first months of the accelerated stability study, present the long-term stability data.

7.5.3.2 For container of 1 ml or less, a water loss of more than 5% from the initial value during the first three months of the accelerated stability study is acceptable if justified.

7.5.4 For medications to be stored under refrigerated conditions, follow the next chart:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	25°C ± 2°C / 60% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability	5°C ± 3°C	12 months	0, 3, 6, 9 and 12 months

7.5.5 For medications to be stored under freezing conditions follow the next chart:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Long-term stability	-20°C ± 5°C	12 months	0, 3, 6, 9 and 12 months

To evaluate the impact of short excursions, outside the conditions established in the label, a pilot lot should be submitted to 5°C ± 3°C or 25°C ± 2°C during an appropriate period, as applicable

8 Known medication

8.1 Selection of lots. See paragraph 7.1

8.2 Container-closure system. See paragraph 7.2

8.3 Parameters to be evaluated and analytical methodology. See paragraph 7.3

8.4 Submit the data obtained in the accelerated stability study according to that indicated in the corresponding chart and the long-term stability data available at the time of making the registration application.

8.5 Conditions of the study. The conditions of the study and its duration shall be enough to cover the storage, distribution and use of the medication; apply any of the following conditions:

8.5.1 General case:

Type of study	Storage conditions	Minimal period	Frequency of analysis
Accelerated stability	40°C ± 2°C / 75% ± 5% RH	3 months	0, 3 and 6 months
Intermediate stability**	30°C ± 2°C / 65% ± 5% RH	6 months	0, 3 and 6 months
Long-term stability*	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH	12 months	0, 3, 6, 9 and 12 months

* It is the decision of the manufacturer to carry out the long-term stability studies at 25°C ± 2°C RH / 60% ± 5% RH or at 30°C ± 2°C RH/ 65% ± 5% RH

** If 30°C ± 2°C RH / 65% ± 5% RH is the long-term stability study condition, then it is not necessary to make the study at the intermediate condition.

Significant changes. See paragraphs 7.5.1.1 and 7.5.1.2

8.5.2 Particular cases. See paragraphs 7.5.2, 7.5.3, 7.5.4 and 7.5.5

For these cases, the minimum period of the accelerated stability study is 3 months and the analysis frequency is 0, 1 and 3 months.

9 General considerations

9.1 The stability study of a medication shall include the tests for the characteristics mentioned as follows in each of the pharmaceutical forms. When the medication does not require some of the indicated tests, its elimination shall be technically supported.

TESTS FOR SOLIDS

	Tablet and pills	Capsule	Reconstitution powder for oral use	Reconstitution power for parenteral use	Powder for topic use	Inhalation powder
Appearance	√	√	√	√	√	√
Colour	√	√	√	√	√	√
Odour	√2	√2	√2	NA	NA	NA
Assay	√	√	√	√	√	√
PH	NA	√1	NA	NA	NA	NA
Disintegration	√3	√3	NA	NA	NA	NA
Dissolution	√2	√2	NA	NA	NA	NA
Hardness	√4	NA	NA	NA	NA	NA
Humidity	√	√2	√	√	√	√
Re-suspendibility	NA	NA	√	√	NA	NA
Reconstitution time	NA	NA	√	√	NA	NA
Preservatives content	NA	NA	√2	√2	√2	√2
Microbial limit (initial and final)	NA	√	√	NA	√	√
Sterility /Pyrogen or bacterial endotoxins (initial and final)	NA	NA	NA	√	NA	NA

1. When the capsule is made of soft gelatin and the content is liquid
2. When applies
3. When the dissolution is not required
4. Only for tablets

Note: In the event of reconstitution powders, once they are reconstituted, the tests corresponding to solutions or suspensions, as the case may be, should be performed during the period and conditions of use indicated on the label.

TESTS FOR SEMI-SOLIDS

	Suppositories and ovules	Topic gelatin, cream and ointment	Otic and ophthalmic gel, cream and ointment
Appearance (including consistency)	√	√	√
Colour	√	√	√
Odour	√	√	√
Assay	√	√	√
pH	NA	√1	√1
Particulate material	NA	NA	√
Loss of weight	√2	√2	√2
Viscosity	NA	√	√
Preservers content	√1	√1	√1
Sterility (initial and final)	NA	NA	√
Microbial limit (initial and final)	√	√	NA

1. As applicable
2. When the primary packing is permeable or semi-permeable

TESTS FOR LIQUIDS

	Oral, topic and nasal solution	Ophthalmic, otic and parenteral solution	Oral or topic emulsion	Parenteral emulsion	Oral, topic or nasal suspension	Ophthalmic and parenteral suspension
Appearance	√	√	√	√	√	√
Colour	√	√	√	√	√	√
Odour	√	√1	√	√1	√	√1
Clarity of solution	√	√	NA	NA	NA	NA
pH	√	√	√1	√1	√1	√1
Assay	√	√	√	√	√	√
Content of preservers (initial and final)	√4	√4	√4	√4	√4	√4
Microbial limit (initial and final)	√	NA	√	NA	√	NA
Sterility (initial and final)	NA	√	NA	√	NA	√
Pyrogen or bacterial endotoxins (initial and final)	NA	√3	NA	√	NA	√3
Weight loss	√2	√2	√2	√2	√2	√2
Resuspendibility	NA	NA	NA	NA	√	√
Sedimentation volume	NA	NA	NA	NA	√	√

1. As applicable
2. When the primary packaging is permeable or semi-permeable
3. When for parenteral use
4. Only for multiple dose medication

OTHER PHARMACEUTICAL FORMS

	Aerosol for inhalation	Nasal spray: solution or suspension	Topic aerosol	Transdermal	Subcutaneous implants, vaginal or intrauterine devices releasing drugs
Appearance	√	√	√	√	√
pH	NA	√1	NA	NA	NA
Assay	√	√	√	√	√
Water content	√	NA	√	NA	NA
Preserver content	√1	√1	√	NA	NA
Adhesion	NA	NA	NA	√	NA
Release speed	NA	NA	NA	√1	√
Assay for co-solvents	NA	NA	√1	NA	NA
Weight loss	√	√2	√	√1	NA
Particle size	√	√1	√1	NA	NA
Microbial limit (initial and final)	√	√	√	√	√1

	Aerosol for inhalation	Nasal spray: solution or suspension	Topic aerosol	Transdermal	Subcutaneous implants, vaginal or intrauterine devices releasing drugs
Sterility (initial and final)	NA	NA	NA	NA	√1

1. When applicable
2. When the primary container is permeable or semi-permeable

9.2 For drugs and medications, it is important to verify that the degradation products observed during the stability studies do not exceed the limits established in the Pharmacopoeia of the United Mexican States and its supplements. When the latter does not contain the information, you may investigate in the pharmacopoeia of other countries, which analysis procedures are made according to the specifications of specialized bodies or other scientific bibliography internationally renown. When the information is not available in any of the above cases, it should be considered that the degradation products do not represent a risk in the safety of the drug or medication.

9.3 If there are other physical, chemical or biological parameters of the medication not mentioned in this standard that are affected during the stability study, they should be determined according to that established by the Pharmacopoeia of the United Mexican States and its supplements. When the latter does not contain the information, you may investigate in the pharmacopoeia of other countries, which analysis procedures are made according to the specifications of specialized bodies or other scientific bibliography internationally renown.

9.4 For the pharmaceutical forms not included in this standard, the physical, chemical, microbiological and biological tests that should be performed during the stability studies are those indicative of stability and that are included in the United Mexican States Pharmacopoeia and its supplements. When the latter does not contain the information, you may investigate in the pharmacopoeia of other countries, which analysis procedures are made according to the specifications of specialized bodies or other scientific bibliography internationally renown.

9.5 In the case of the medication where the manufacturer indicates that for its administration they may or may not be mixed with another medication or other substance, the stability study should be performed from the obtained mixture, according to the preservation conditions indicated on the label.

9.6 In dealing with biological products, apart from the parameters of the described pharmaceutical form, it is necessary to evaluate its strength as biological activity, according to that established by the Pharmacopoeia of the United Mexican States and its supplements. When the latter does not contain the information, you may investigate in the pharmacopoeia of other countries, which analysis procedures are made according to the specifications of specialized bodies or other scientific bibliography internationally renown.

9.7 If the stability studies presented to obtain the registration, under the conditions established in this document, are satisfactory, a tentative shelf life of 24 months shall be granted.

When due to the characteristics of the drug or medication, different conditions than the ones indicated in paragraphs 5.4 6.4, 7.5 and 8.5 are required to carry out the stability

study they shall be technically supported and make previously the protocol with the sanitary authority.

9.8 The long term stability of the lots submitted in the registration file should continue until reaching the shelf-life granted in the registry of the medication. The analysis of the samples should be performed every 3 months during the first year and every 6 months in the second year, and report the results to the sanitary authority

9.9 If the lots submitted in the registration file are pilot lots, after the registration is granted, the first three production lots should be submitted to a long-term stability. The analysis of the samples should be performed every 3 months during the first year and every 6 months in the second year, and annually afterwards for a maximum period of 5 years.

9.10 Annual stability program. One year after manufacturing the first three production lots, an annual program should be implemented for the registered and commercialized medications in order to monitor the stability characteristics. Submit a lot of each strength in each container-closure system approved under the long-term stability conditions, in all subsequent years in which they are manufactured.

9.11 In the long-term stability cases and annual program, reduced analysis designs may be applied if justified.

9.12 When a medication has the same qualitative formula in the same packaging material, in presentations with different drug concentrations, at least the results from the stability study of the presentation with the lesser and the major drug concentration should be submitted.

9.13 For import medications, the tentative expiry date shall be confirmed with the long-term stability studies, of samples stored and analyzed in Mexico. Exceptions should be concerted and evaluated with the Health Department.

9.14 The stability data obtained from the long-term stability studies of the first three production lots or from the annual program may be used to apply for an extension of the shelf-life of the medication.

9.15 If a drug or additive remains stored according to the conditions indicated on the label, after the analysis date established, it can be reanalyzed to prove that it complies with its specifications and used during a period no longer than 30 days after the analysis. The drug or additive may be analyzed several times and use it meanwhile it complies with the established specifications.

9.16 Stability studies for changes to the registration conditions

9.16.1 The changes included in this standard are:

9.16.1.1 Components or composition of the formulation

9.16.1.2 Lot size

9.16.1.3 Manufacturing

9.16.1.3.1 Equipment

9.16.1.3.2 Process

9.16.1.4 Changes in the drug

9.16.1.5 Container-closure system

9.16.2 Perform the corresponding stability study, according to Appendix A and submit the data together with the application for the modifications to the registration condition

9.17 When a drug or medication lot is reprocessed or reworked, as the case may be, the information must be signed by the person responsible for the sanitary area. When the reprocessing or reworking includes significant changes from the original process, the stability of the lot should be confirmed with an additional analysis at the maximum time of the accelerated stability condition, that demonstrate that the specifications of the product are not modified.

9.18 When the analytical method is changed during the stability study, it should be demonstrated that the two methods are equivalent through the validation process.

9.19 All analysis carried out during the stability study shall be made in duplicate and be reported with stability indicative methods.

9.20 Protocol of the study. It shall contain the following information:

9.20.1 Name of the drug or medication, pharmaceutical form, presentation and concentration.

9.20.2 In the case of the medications, the manufacturer and technical grade of the drug and additives

9.20.3 Type, size and number of lots

9.20.4 Description of the container-closure system

9.20.5 Conditions of the study

9.20.6 Sampling time and analysis

9.20.7 Test parameters

9.20.8 Stability specifications

9.20.9 Reference to analytical methods per parameter, and its validation, if necessary.

9.20.10 Reduced analysis design, if justified.

9.20.11 Name and signature of the sanitary responsible

9.21 Study report. It shall contain the following information:

9.21.1 Name of the manufacturer of the drug and/or medication

9.21.2 Name of the drug or medication, pharmaceutical form, presentation and concentration

9.21.3 Number and size of the lots and manufacturing date

9.21.4 Description of the container-closure system

9.21.5 Analytical tabulated data per storage condition and date of initiation and end of study

9.21.6 Chromatograms or spectrograms representatives of the stability mounted lots at the beginning and end of the study, if applicable.

9.21.7 Conclusions

9.21.8 Proposal for the shelf-life

9.21.9 Name and signature of the sanitary responsible

9.22 For medication with new drugs, during clinical studies in phase I, II and III, the manufacturer should demonstrate the stability of the clinical material until the maximum time of the study.

10 Concordance with international standards

This norm is not equivalent to any other international or Mexican standard

11 Bibliography

11.1 General Health Law, Mexico. Official Gazette of the Federation, February 7, 1984 and its amendments up to June 28, 2005

11.2 Federal Law on Metrology and Normalization.- Mexico, Official Gazette of the Federation, July 1, 1992 and its reforms and additions up to May 19, 1999

11.3 Regulation on Health Items.- Mexico. Official Gazette of the Federation, February 4, 1988 and its reform dated September 19, 2003

11.4 Regulations from the Federal Law on Metrology and Normalization.- Mexico Official Gazette of the Federation, January 14, 1999

11.5 Regulation of the Federal Commission for the Protection against Sanitary Risks.- Mexico: Official Gazette of the Federation, April 13, 2004

11.6 Pharmacopoeia of the United Mexican States, edition in force and its Supplements.

11.7 FDA/ CDER Guidance for Industry: Stability Testing of Drug Substances and Drug Products (Draft, June 1998)

11.8 ICH Q1A (R2): stability Testing of New Drug Substances and Products (Feb. 2003)

11.9 ICH Q1C; Stability Testing for New Dosage Forms (Nov. 1996)

11.10 ICH. Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (Feb 2002)

11.11 Canada /TPP Guidance for Industry: Stability Testing of Existing Drug Substances and Products (Sept. 1997 / Draft 02)

11.12 ICH5C: Quality of Biotechnological Products: Stability Testing of Biotechnological /Biological Products.

11.13 SUPAC, Immediate Release Solid Oral Dosage Forms: Chemistry, Manufacturing and Controls, In Vitro 1 dissolution Testing, and In Vivo Bioequivalence Documentation.

11.14 Drug Stability: Principles and Practices, Carstensen and Rhodes, Third Edition, USA 2000

11.15 International Pharmaceutical Product Registration: Stability Data, Cartwright $ Mathews, USA 1995

11.16 ICH Q3(R): Impurities in New Drug Substances (Feb 2002)

11.17 ICH Q3B(R): Impurities in New Drug Products (Fe 203)

11.18 ICH Q3C: Impurities Residual Solvents (Dec 1997)

11.19 Guidance for Industry (FDA/ CDER)

11.19.1 ANDAs: Impurities in Drug Products (Dec. 1998)

11.19.2 ANDAs: Impurities in Drug Substances (Nov. 1999)

11.20 Guidance for Industry (Canada / TPP): Identification, Qualification and Control of related Impurities in Existing Drugs (April 1999, Draft No. 4)

12 Observance of the Standard

The surveillance of compliance with this standard corresponds to the Health Department. The personnel from this department shall perform the necessary surveillance and verification.

13 Period in force

This Official Mexican Standard shall enter in force 120 natural days following the date of its publication in the Official Gazette of the Federation.

Mexico, D.F. October 20, 2005 .- The President of the National Consultative Committee on Sanitary Normalization, Regulation and Sanitary Development, **Ernesto Enríquez Rubio.** Signature

APPENDIX

Changes to the registration conditions

Type of Change	Level 1	Level 2	Level 3
Components or composition of the formulation	1 long-term lot	1 lot of 3 months of long-term and accelerated stability	If there are previous studies*: One lot of 3 months of long-term and accelerated stability
			If there are previous studies*: Three lots of 3 months of long-term and accelerated stability
Lot size	1 long-term lot	1 lot of 3 months of long-term and accelerated stability	
Manufacturing Equipment	1 long-term lot	If there are previous studies*: 1 lot of 3 months of long-term and accelerated stability	
		If there are no previous studies*: 3 lots of 3 months of long-term and accelerated stability	
Manufacturing Process		1 lot of 3 months of long-term and accelerated stability	If there are previous studies*: 1 lot of 3 months of long-term and accelerated stability
			If there are no previous studies*: 3 lots of 3 months of long-term and accelerated stability
Drug			3 lots of 3 months of long-term and accelerated stability
Container Closure System	1 long-term lot	1 lot of 3 months of long-term and accelerated stability	3 lots of 3 months of long-term and accelerated stability

* Previous studies concerning the stability of the medication, meaning that there are data of five years of commercial experience for new medications, or else, three years for known medications.