Ministry of Health
Executive Decree Nº 504
(Dated 9 November 2005)

"Whereby Stability Study Standards are regulated as indicated in Law Nº 1 dated 10 January 2001, and are enforced and other provisions revoked."

The President of the Republic,
Applying his constitutional and legal powers,

WHEREAS:

Paragraph 14 of Article 184 of the Political Constitution establishes that it is a function of the President of the Republic, with the participation of the respective Minister, to regulate the laws that so require for better enforcement, without losing sight of their text or their spirit.

Law Nº. 1, dated 10 January 2001, regulates matters of Medications and other products for human health.

The World Health Organisation and the International Conference on Harmonisation have adopted modifications for stability studies for pharmaceutical products for Climatic Zones III and IV.

Panama belongs to Climatic Zone IV, which is the most critical in matters of temperature and humidity, which represent a risk factor for drug stability.

Executive Decree No. 178, dated 12 July 2001, regulates Law Nº. 1, dated 10 January 2001, and considers stability norms in Title II, Chapter I, Section III.

The National Pharmacovigilance System receives notifications of pharmaceutical failures attributed to stability problems, so that it has become necessary to adapt the pertinent provisions for stability studies required by pharmaceutical products.

DECREES:

Article 1. This Decree regulates the norms for stability studies for pharmaceutical products as indicated in Law Nº. 1, dated 10 January 2001.

Article 2. For the purposes of this Decree, the following definitions will be in effect:

1. Bracketing: Design of a stability programme in which samples of only the extremes of certain design factors, for example, strength or container size, are analysed at all time points under a complete study design. This design supposes that the stability of any of the intermediate levels is represented by the results of the analysed extremes. This design is applicable when a medication has the same qualitative formula, in the same package, in presentations with different concentrations of the drug, it will be possible to present the results of the stability study of the presentations with the lowest and highest concentration. The design may be applied to recipients of different sizes or different contents with the same container-closure system.

2. Semi-permeable packaging, recipients or containers: Those allowing the passage of a solvent, usually water; however, they do not allow the loss of the solute. Examples of these containers include plastic bags; semi-rigid low density polyethylene bags used for large volume parenteral products; low density polyethylene ampoules, vials and bottles

3. Physical and physicochemical stability: The ability of a pharmaceutical product to remain within the specified limits for appearance, colour, odour, palatability, texture, dosage uniformity, re-dispersability, moisture, friability, hardness, disintegration, pH, dissolution and other characteristics, according to the product's pharmaceutical form.

4. Microbiological and biological stability: The ability of a pharmaceutical product to remain free from microorganisms or within the allowed range.

5. Chemical stability: The ability of the active principal to conserve its identity, purity, concentration or strength, within the range of the official specifications or those stipulated by the manufacturer.

6. Accelerated stability study: A study designed to increase the speed of the chemical or physical degradation of a packaged product in its final packaging for market employing extreme storage conditions. The purpose of these studies is to predict the shelf life of the pharmaceutical product and/or determine the kinetic parameters of the degradation processes, under long-term or real-time storage conditions for Panama. The design of these studies includes high temperatures, high humidity and exposure to intense light. The results from accelerated stability studies must be complemented by stability studies carried out under long-term or real-time actual storage conditions in Panama.

7. Long-term or real-time stability study: Designed to determine over the long-term the physical, chemical, physicochemical, microbiological or biological characteristics (the last two, when applicable), of the formulation packaged in its final packaging for market, under conditions established or harmonized for Climatic Zone IV, or under special storage conditions, for example: refrigeration at 5 ± 3 ºC. The purpose of these studies is to set, verify or extend the term for the shelf life of a pharmaceutical product.

8. Expiration date or expiry: That which is placed on the primary and secondary packaging of a pharmaceutical product, to indicate the date until which it is expected that the product will satisfy the quality specifications. This date is established for each lot by adding the shelf life to the date of manufacture.

9. Lot or batch: A quantity of raw materials or pharmaceutical product that is processed in a manufacturing cycle or series of cycles, until its final form has been reached. The essential characteristic of a lot is its homogeneity.

10. Industrial or production lot: That lot destined for the usual purpose of sale or distribution.

11. Pilot lot: That lot produced for experimental purposes, usually no less than 10% of the standard size of the production lot; it is produced following the same general manufacturing method and employing equipment that are representative of the process or the same ones that are used on an industrial scale.

12. Raw materials: Those active or inactive substances that are used for the manufacture of pharmaceutical products, whether they remain unaltered, undergo modification or are eliminated during the manufacturing process. Conditioning materials are excluded.

13. Matrixing: A statistical technique that is used to carry out stability studies whereby, a selected subset of the total number of possible samples for all product factors will be tested at a specified time point. The next time point will test another subset of the total number of possible samples. This design assumes that each subset tested is representative of all of the samples at the given time point, so that in the following analysis time point another, different, set of samples is selected, and so forth, until the end of the study.

14. Verified shelf life: Time, in years or months, of the shelf life of the product, as determined by long-term or real-time stability studies or those carried out under storage conditions harmonised for Climatic Zone IV, adopted for Panama or special storage conditions, for example, refrigeration at 5 ± 3 ºC.

15. Tentative shelf life: Shelf life period established in a provisional manner, estimated by extrapolation or projection of data coming from short-term accelerated stability studies, for a minimum of 6 months, carried out with the product packaged in its packaging for market. This period is subject to verification and allows the approval of up to twenty-four (24) months of shelf life.

16. Finished product: A pharmaceutical product that has passed through all production phases, including conditioning in its final container and labelling. The finished product constitutes the medication that is placed on sale.

17. Shelf life: The ability of a product or an active principal to maintain its original properties within the established specifications, in respect of its identity, concentration or strength, quality, purity and physical appearance, for a predetermined period of time.

18. Climatic Zone IV: Tropical area or region where hot and humid environmental conditions prevail.

Article 3. All pharmaceutical products requesting health registry for the first time must present stability studies for the finished product, in order to set a shelf life and expiration date, pursuant to the provisions established in this Decree. Innovative products must also include stability studies of the active principal.

Paragraph: The stability studies for products sensitive to the conditions in Climatic Zone IV will be evaluated at each renewal period.

Article 4. Stability studies of the finished product, packaged in its marketing package, must include information on:

a) Physical and physicochemical stability;
b) Chemical stability;
c) Biological and microbiological stability, when applicable.

Article 5. Stability studies of the active principal must include information on its physical, chemical, biological and microbiological stability, the latter two when applicable, and that serve as the basis for its approval in the country of origin. Information on degradation products and other sub-products must be included, as well as the mechanisms of degradation of the active

principal, isolation, identification, quantification and permissible limits of the degradation products. This only applies for the active principals that do not appear in the official bibliographic references.

If the presence of impurities from synthesis is relevant for the stability of the active principal or the products containing it, the corresponding available information must be included.

Article 6. Products already registered that, as of the date this Decree is promulgated, do not have stability studies in their dossier and present notifications of suspicion of pharmaceutical or therapeutic failures, must present these stability studies when required to do so by the Health Authority.

Article 7. Stability studies must be presented if, after health registration, there have been changes in:

1. Container-closure material, type of container-closure and/or the container-closure system;
2. The qualitative and quantitative composition of the product;
3. The manufacturing process and/or a change in the manufacturing equipment and primary conditioning of the product;
4. Changes in product specifications;
5. The stability protocol; or
6. Other factors that might affect the product's stability.

Paragraph: It will not be necessary to present product stability studies when the formula is modified quantitatively, in respect of the amounts of excipients, up to a maximum of 10%, as against the total formula weight; in liquids this may be in respect of weight or volume.

Article 8. The following types of stability studies will be accepted:

1. Long-term or real-time stability studies,
2. Accelerated stability studies.

Article 9. The long-term or real-time studies must be carried out under controlled storage conditions, at a temperature of 30 ± 2 ºC and a relative humidity of 70 ± 5% or 65 ± 5%, or those storage conditions harmonized for Climatic Zone IV that Panama may adopt posterior to the stipulations of this Decree.

The study conditions for products requiring refrigeration must be a temperature of 5 ± 3 ºC.

The study conditions for products for aqueous base products stored in semi-permeable recipients must be a temperature of 30 ± 2 ºC and a relative humidity of 35 ± 5%.

Article 10. The Decree hereby sets an analytical frequency that includes four (4) measurements for the first year, including the starting point, the final point and two intermediate points; every six (6) months for the second year; and a minimum of annual measurements for the following years, until the shelf life proposed by the manufacturer has been completed.

The duration of the long-term or real-time studies must be equal to the proposed shelf life. These studies are the only ones accepted for granting verified shelf life periods for products.

The maximum shelf life that can be granted is 5 years, as long as the product has presented long-term or real-life stability studies, as stipulated in this regulation.

Article 11. For products sensitive to Climatic Zone IV conditions, long-term or real-time stability studies will be accepted that have been carried out at a temperature of 25 ± 2 ºC and a relative humidity of 60 ± 5% in either of the following conditions:

1. The product is for intra-hospital use.

2. The drug is not available on the local market in response to a health problem.

In either of these cases, it must be shown by means of studies carried out at a temperature of 30 ± 2 ºC and a relative humidity of 70 ± 5% or 65 ± 5% pursuant to these norms that product quality is significantly affected and that there is no other product that has been shown to be stable under these conditions.

Article 12. The studies carried out at a temperature of 25 ± 2 ºC and relative humidity of 60 ± 5% for the products mentioned in the preceding article must comply with the rest of the requirements described in this Decree, and they are granted a maximum shelf life of 24 months. In these cases, the distributor(s) of the product may only market it in those establishments that meet the storage conditions established for this type of product. Breach of this condition will be considered a serious fault.

Article 13. The accelerated stability studies must be carried out under controlled conditions at a temperature of 40 ± 2 ºC and a relative humidity of 75 ± 5%, for six months or other climatic conditions harmonised at the international level and adopted by Panama, which may be dated after this Decree.

The study conditions for pharmaceutical products requiring refrigeration must be at a temperature of 25 ± 2 ºC and a relative humidity of 60 ± 5%, for six (6) months.

The study conditions for pharmaceutical products that require freezing must be at a temperature of -20 ± 5 ºC for a period of not less than twelve (12) months.

Article 14. For accelerated studies, as described in the foregoing article, the analytical frequencies established by the World Health Organisation or by the International Conference on Harmonisation will be accepted, or as a minimum, an analytical frequency that includes the starting point, the end point and an intermediate point.

Accelerated stability studies allow assignment of a shelf life of up to twenty-four (24) months for marketing. In these cases, the manufacturer undertakes to present long-term or real-time stability studies for the approved period. Were this acquired commitment not met, the sanctions typified in the law will be applied.

Article 15. In liquid and semi-solid products, the requirement for controlled relative humidity may be ignored when carrying out accelerated stability studies, when these products are contained in primary packaging that imposes a barrier to water vapour, to wit, totally impermeable packaging.

Article 16. If the results of the accelerated stability studies indicate significant changes to the product, a tentative shelf life may not be granted to the product, rather, long-term or real-time studies for the product must be presented for the requested shelf life.

Article 17. A significant change to the product has occurred when accelerated stability study outcomes show that:

1. The assay of the content or strength shows that there has been a 5% reduction in comparison with the initial results for a lot.
2. Any degradation product exceeds the acceptance criteria.
3. Product pH falls outside the pre-set limits.
4. Specified limits for the dissolution of twelve (12) tablet or capsule units of the product are not met.
5. The microbial limits set are exceeded.
6. The acceptance criteria for appearance, physical tests and functional assays, for example, colour, phase separation, re-suspension, hardening, hardness and modified dose release are not met; however, some changes may occur in the physical attributes, for example, softened suppositories and melted crèmes, which are expected under accelerated conditions.

Article 18. The labelling of the secondary packaging must bear the printed information referring to the storage conditions, specifying the temperature and, where necessary, indicate that it must be protected from light. If the product does not have secondary packaging, all required information must be printed on the primary packaging.

Article 19. To maintain the assigned shelf life in the health registry, after any of the changes indicated in Article 6 has occurred, when the stability information presented does not cover the period or there is no information available, the manufacturer must undertake one of the following:

1. Carry out accelerated studies and continue with the long-term or real-time studies for the duration of the assigned shelf life, in the first three production lots, if the stability information presented is based on a long-term or real-time stability study, but this has not completed the full shelf life as assigned in the registry.
2. Carry out accelerated studies and continue with the long-term or real-time studies, adding additional production lots, for a total of at least three, and continue them until the assigned shelf life has been fulfilled, if the information presented was based on a long-term or real-time stability study in less than three post-change production lots.
3. Carry out long-term or real-time stability studies and present the results when the assigned shelf life has been fulfilled, if the stability information presented was based on an accelerated stability study of three lots.
4. Undertake an accelerated stability study and a long-term or real-time study of the first three post-change production lots and present the results upon completion of the assigned shelf life, if there are no long-term or real-time or accelerated stability studies.

The interim reports of the long-term or real-time studies must be submitted every six months during the first two years and annually during the following years. The interim reports from the accelerated studies must be presented before completion of the first year after having assumed the commitment; otherwise, the health registration will be suspended until the acquired commitment has been met.

Article 20. Registered pharmaceutical products for which no quality problems have been verified, and that later undergo a change of country or manufacturing site, or that change the place and/or packing laboratory, or a new health registry, and that do not have stability studies with the product manufactured in the plant located in the new country, site and/or primary packaging laboratory, will be assigned the same shelf life duration, as long as the manufacturer submits stability study data for 6 months of accelerated stability data and one of the commitments described in the foregoing article.

Article 21. Documentation for the stability studies must include the study protocol, a summary of the results and the individual results from each lot studied. This information must be submitted in Spanish. There follows a listing of the minimum requirements for the documentation indicated above:

1. **Study Protocol:**

a. The stability study must include the name and signature of the professional responsible for the study, as well as the name of the laboratory and country where the study was carried out.
b. The design must define whether the storage area has temperature and humidity controls, sampling frequency and number of samples to be analyzed in each sampling period for each lot, and type of tests to be carried out within each sampling period.
c. The study must be carried out on a minimum of three lots, one of which must be at least a pilot or industrial lot, prepared with the same formula, primary packaging, manufacturing process and general conditions declared for industrial lots. The lots utilised in the study must have been manufactured in the same country and plant as the product for which health registry is sought. The size of each lot utilised in the study must be stated.
d. The study must be carried out on each one of the packaging and closure systems proposed for marketing in each presentation. The National Pharmacy and Drug Office (*Dirección Nacional de Farmacia y Drogas*) may accept stability studies with reduced designs, using bracketing and matrixing techniques, pursuant to the guidelines of the International Conference on Harmonisation (ICH).
e. In the case of solid products that must be reconstituted prior to use, such as powders for suspension or solutions for oral use, injectables and others, a stability study must also be carried out with the reconstituted product, which will validate the shelf life of the product after reconstitution, for different storage conditions, recommended in the labelling. Those products that must be completely utilised immediately after reconstitution are excluded.
f. In the case of injectables delivered with their diluent, the set, drug + diluent, must be submitted to the same storage and sampling conditions and analytical tests. The shelf life must be applied to the set, drug and diluent.
g. The scope of the tests carried out in each sampling period must allow determination of the chemical, physical, physicochemical, biological and microbiological stability. All product characteristics with a probability of being affected by storage must be considered.
   For sterile products, it is understood that sterility tests and, where necessary, that for pyrogen limits, will be carried out only as compulsory quality control tests for lot release and approval
h. The procedures for un-official analytical tests must be thoroughly validated and the results of the analyses must be stability indicators.

i. The analytical methodology utilised and its source must be indicated. If the methodology is un-published, it must be described in detail. If there are pre-set specification limits for any degradation product or other relevant impurities for stability, this method must also include those aspects corresponding to their quantification. In the case of related substances and/or degradation products, these are determined solely if the product monograph so requires.
j. Describe the mathematical and statistical treatment of the results regarding product concentration or strength for calculating tentative shelf life.

2. Summary of the results: A summary of the study carried out must be submitted, which will indicate, as a minimum, the following information:

a. Product name, concentration, pharmaceutical form, manufacturer's name, place and country of manufacture. In the event that the product is conditioned by another laboratory, the conditioning laboratory's name, location and country must be indicated.
b. Type of container-closure and characteristics of the container-closure material.
c. Data on the lots studied, which includes type of lot, such as experimental, pilot or production, number, size and date of manufacture.
d. Dates corresponding to initiation and termination of the study.
e. Data corresponding to finished product specifications.
f. Type of study, long-term / real-time or accelerated and the storage conditions under which the study was carried out.
g. Summary of the chemical, physical and physicochemical, microbiological and biological characteristics or changes encountered.
h. Indicate the requested shelf life and storage conditions defined for the product.
i. Name, position and signature of the person responsible for the study.

3. Results of each lot studied: The documentation for each lot studied must contain, as a minimum, the following information, preferably in tables:

a. Product name, concentration, pharmaceutical form, manufacturer's name, place and country of manufacture. In the event that the product is conditioned by another laboratory, the conditioning laboratory's name, location and country must be indicated.
b. Type of container-closure and characteristics of the container-closure material.
c. Lot number, size, date of manufacture and type of lot.
d. Dates corresponding to initiation and termination of the study.
e. Temperature and relative humidity, if applicable, under which the study was carried out.
f. Data corresponding to finished product specifications.
g. The individual results regarding product strength obtained at each sampling time point, expressed in absolute values or percentages, in respect of the label claim. The average ± standard deviation at each sampling time point must also be included.
h. Quantification of the degradation products, in the same terms and units employed for the active principal, when there are specified limits, or in different units, as long as these are clearly specified in the documentation. If the concentrations are not quantifiable, the results must be referred to the detection limits of the method.
i. The mathematical and statistical treatment of the product concentration results must be presented in a detailed and graphical form, for the absolute data for each lot, in order to set the shelf life. Presentation of this information will only be compulsory in

the event that the National Pharmacy and Drug Office so requires, as a document necessary for further analysis of the stability studies.

j. Results of the physical and physicochemical essays and their corresponding specifications.
k. Results of the sterility and pyrogen limit tests carried out for lot release and approval, where applicable.
l. Results of preservative challenge studies, in order to demonstrate that their activity continues through to the end of the shelf life, in the case of the medications in which preservative concentration is a critical parameter, for example, collyria, multiple-dose injectables and others.

Article 22. The requests for Health Registry that are in process when this Decree becomes effective may request that their stability studies be evaluated under the present provision.

Article 23. The stability norms regulated under this Decree must be reviewed every two (2) years.

Article 24. The Decree revokes Articles **44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55** and **56** of Executive Decree Nº. 178, dated 12 July 2001, as well as any provision that may be contrary hereto.

Article 25. The Decree will go into effect upon promulgation in the Official Gazette.

Issued in the City of Panama, on the 9th day of November in the year two thousand five (2005).

To be communicated and enforced.

[Signed]
Martin Torrijos Espino
President of the Republic

[Signed]
Camilo A. Alleyne
Minister of Health