RDC RESOLUTION NO. 50, SEPTEMBER 20, 2011

DOU Sept/22/2011

Stipulates the procedures and conditions for conducting stability studies for registration or changes post-registration of biological products and establishes other measures.

The Collegiate Board of Directors of the National Health Surveillance Agency, as per the attribution granted it in paragraph IV of Art. 11 of the Regulation approved by Decree no. 3.029, of April 16, 1999, and taking into account what is stipulated in paragraph V and §§ 1 and 3 of Art. 54 of the Internal Bylaws approved as per the terms of Annex I of ANVISA Administrative Rule no. 354, of August 11, 2006, republished in the Official Federal Gazette on August 21, 2006, at a meeting held on November 20, 2011,

adopts the following Collegiate Board of Directors Resolution, and I, Chairman – President, determine its publication:

CHAPTER 1
OF THE INITIAL PROVISIONS

Section 1
Objective

Art. 1 - This Resolution stipulates the procedures and conditions for conducting stability studies for registration or changes post-registration of biological products.

Section II
Definitions

Art. 2 – For the purposes of this Resolution, the following definitions are adopted:

I – grouping: this is the stability plan model where samples of the extremes of certain factors, such as dosage and package size, are tested. The model assumes the stability of any intermediate factor is represented by the tested extremes;

II – level 1 change (minor change): these are post-registration changes of lesser complexity that could be implemented with ANVISA's prior authorization;

III – level 2 change (moderate change): these are post-registration changes of average complexity, which need ANVISA's prior authorization for implementation;

IV – level 3 change (major change): these are post-registration changes of higher complexity, which need ANVISA's prior authorization for implementation;

V – reduced design: these are stability studies the samples of which are not tested at every analysis time for each combination factor (ex: concentration and volume, type of primary packaging and volume, among others), such as grouping and matrixing;

VI – follow-up study: this is a stability study conducted to ensure the pharmaceutical product maintains its physical, chemical, biological and microbiological characteristics as per the results obtained in long-duration stability studies;

VII – accelerated stability study: this is a study designed to accelerate chemical and biological degradations and/or physical changes of a pharmaceutical product in forced conditions of storage;

VIII – cumulative stability study: this study determines the effect of the storage period for the active principle, the intermediate product and/or product in bulk on the quality of the finished biological product;

XI – long-duration stability study: this study is designed to evaluate the physical, chemical, biological and microbiological characteristics of a pharmaceutical product during and, optionally, after the expected expiration date. The results are used to establish or confirm the stipulated expiration date and recommend storage conditions;

X – partial long-duration stability study: this is a long-duration stability study with partial results, where the final report should be submitted to ANVISA in the change history;

XI – stress study: this study is designed to evaluate the impact of short exposures to conditions outside of those established on the product label, which may occur during transportation and/or storage;

XII – stability in use study; this refers to evaluating the maintenance of quality, safety and effectiveness of the product in real use situations (ex: reconstitution, dilution, infusion, removal of the product from multi-dose packages), simulating product conservation conditions for the period of time recommended by the manufacturer;

XIII – photostability study: this study is designed to detect significant changes in the product after exposure to light;

XIV – impurity: this is any component of the active substance or of the finished biological product, which is not the chemical entity defined as an active substance, an excipient or other additive of the finished biological product;

XV - matrixing: this is the stability plan model in which a sub-group of total available samples is tested at a specific frequency. The model is representative of all possible combinations of factors. In subsequent time intervals, another sub-group of samples is tested for all combination factors. The model assumes that the stability of each sampling's sub-group represents the stability of all samples in a specific time interval. The differences in the samples should be identified as: doses, concentrations, different sizes of a same type of packaging and types of containers;

XVI – indicative profile of stability: this is the set of studies and data that permit identifying significant changes that end up occurring in the product;

XVII – expiration date: this is the date stipulated on the packaging material of the active principle or finished product, designating the time during which a lot of the active principle or of the finished product is expected to remain within specifications, as long as stored in those conditions defined, and after which it should not be used;

XVIII – biological product: this is the biological medication that is not new or is known to contain a molecule with a known biological activity, already registered in Brazil, and which has undergone all manufacturing phases (formulation, bottling, lyophilization, labeling, packaging, storage, quality control and release of the lot of the biological product for use);

XIX – biological product in bulk: this is the biological product that has completed every phase of production, formulated in its final pharmaceutical form, in bulk, kept in a single, sterile container, if applicable, and released by the manufacturer's quality control;

XX – biological product in its primary packaging: this is the biological product that has completed every phase of production, formulated in its final pharmaceutical form, kept in its final container (primary packaging), if applicable, without including the labeling and packaging process and released by the manufacturer's quality control;

XXI – intermediate biological product: this is a pharmaceutical product, of biological origin, partially processed, feasible for specification and quantifiable, which may be submitted to the subsequent phases of manufacturing, before becoming a product in bulk;

XXII – new biological product: this is the biological medication that contains a molecule with a known biological activity, not yet registered in Brazil, and which has undergone all manufacturing phases (formulation, bottling, lyophilization, labeling, packaging, storage, quality control and release of the lot of the biological product for use);

XXIII – finished biological product: this is the pharmaceutical product, of biological origin, which has completed every phase of production, including final packaging, when this provides some sort of protection to the product;

XXIV – degradation products: these are impurities that result from chemical alterations that appear during storage of the medication due to the effects of light, temperature, pH, humidity and characteristics inherent to the active principle, of the reaction with excipients or due to the product’s contact with the primary packaging;

XXV – diluted product: this is the finished biological product with a diluting agent, where the main objective is to reduce the concentration of the final product for administration to the user;

XXVI – reconstituted product: this is the finished biological product obtained by adding solvent for subsequent administration to the user;

XXVII – climate zone: this is the geographically delimited space or zone in accordance with applicable temperature and humidity criteria when conducting the stability studies. Brazil is located in Climate Zone IVb (hot/very humid).

CHAPTER II
OF GENERAL PROVISIONS

Art. 3 – The following information should be included in the stability studies report:

I – manufactured date and the number of lots used;

II – specification for primary packaging;

III – the identification of manufacturers of active principles and finished products used; and

IV – the size of the industrial lots and of the lots used in the stability study.

Single paragraph. The production process and lot size used in the stability study should be representative of those used on an industrial scale.

Art. 4 – The stability studies should contain the analyses that refer to physical-chemical, biological and microbiological characteristics.

Art. 5 – The manufacturer should propose an indicative profile of stability that permits safety in detecting alterations in identity, purity and strength of the product.

Art. 6 – The owner of the registry should inform start and end dates for stability studies or send a timetable with the projected end of the study, in cases involving the submission of partial long-duration stability studies.

Single paragraph. If partial data are submitted for long-duration stability studies, the owner of the registry should send a declaration committing to complementing the stability report within the deadline determined in the body of this article.

Art. 7 – In cases where the product is commercialized in presentations that differ in volume, mass and concentration and the excipients used in the formulation are the same, it is possible to opt for the use of reduced designs.

Single paragraph. The studies submitted for evaluation should be representative of stability for all pharmaceutical forms, presentations, packing and concentrations available for commercialization.

Art. 8 – The final report for the long-duration stability study should be sent to ANVISA as part of the product's next history of change, soon after conclusion of the study, in accordance with legislation currently in effect.

Single paragraph. If the final report is not presented as stipulated in the body of this article, the validity period will be reduced to the proven period, the results of which have already been sent to ANVISA.

Art. 9 – Together with the stability report, the company should also present validation of the methods related to the evaluation of the stability profile that are not included in official compendiums recognized by ANVISA.

Single paragraph. If these validations have already been presented in the registration of the product and there have been no alterations in the methodology, they do not need to be sent again.

Art. 10. If the long-duration stability studies conducted in the conditions established in this resolution prove, at any time, a validity period shorter than the one established in product registration, the company should protocol a post-registration alteration to reduce the validity period in accordance with the data obtained.

Single paragraph. The area responsible for evaluating registration requests and post-registration alterations of biological products should be contacted immediately for the proper measures related to reduction of the validity period, as well as those related to the already commercialized product with an improper validity period.

Art. 11. Exceptionally for products whose use is restricted to hospitals, stability studies in conditions different from those shown in Annex II of this Resolution may be accepted, as long as it is duly proven that the product does not support those conditions established for zone IVb.

Art. 12. The owner of product registration should ensure the recommended conservation during transportation, storage and distribution of the product.

Art. 13. All complementary documentation for stability should be sent to ANVISA as part of the product's history of change, in accordance with legislation currently in effect.

CHAPTER III
OF CONDUCTING STABILITY STUDIES

Section 1
Of the Temperature and Humidity Conditions for the Stability Study on the Active Principle, the Intermediate Product and the Product in Bulk

Art. 14. The suggested temperature and humidity conditions for the accelerated and long-duration stability studies of the active principle, the intermediate product and the product in bulk are shown in Annex I.

Art. 15. The temperature to be used in the accelerated and long-duration stability study of the active principle, the intermediate product and the product in bulk will be determined by the climate zone in which the country of origin is located.

Art. 16. In the case of an imported active principle, intermediate product or product in bulk, the stability studies conducted should follow what is stipulated in Annex II of this Resolution.

Single paragraph. Alternative conditions, when justified, may be accepted for the stability study of the active principle, the intermediate products and the product in bulk.

Art. 17. For products packed in waterproof containers, the stability studies may be conducted under any condition of relative humidity.

Art. 18. The accelerated stability study does not apply to active principles, intermediate products and product in bulk stored at -70°C or -80°C.

Art. 19. If significant changes are observed at any moment when conducting the accelerated stability study, the validity period will be determined by the long-duration stability study.

§ 1 – In general, significant changes are considered to be:

I – a change equal to or greater than 5% of the assay in relation to its initial value, or noncompliance with strength or activity acceptance criteria when biological or immunological procedures are used;

II – detection of the degradation product exceeding acceptance criteria;

III – noncompliance with acceptance criteria for tests of appearances, physical attributes and functionality (ex: color, separation phase, hardness, resuspension, etc.);

IV – noncompliance with acceptance criteria for pH; or

V – noncompliance with acceptance criteria for dissolution of 12 (twelve) dosage units.

§ 2 – It is necessary to give continuity to the accelerated stability study until the 6th (sixth) month, when a significant change occurs in the first 3 (three) months of study.

Section II
Of the Temperature and Humidity Conditions for the Stability Study on the Finished Biological Product

Art. 20. The general temperature and humidity conditions for the stability study of finished biological products should meet the conditions shown in Annex II.

§ 1 - For finished biological products packed in waterproof containers, the stability studies may be conducted under any condition of relative humidity.

§ 2 – For water-based products packed in semi-waterproofed containers, the stability studies should evaluate the possibility of water loss. In this case, the studies should be conducted in conditions of relative low humidity, as described in Annex III.

§ 3 – Other methods may be used to calculate water loss, as long as the scientific reasoning is sent and the calculations are duly justified.

Art. 21. For finished biological products packed at -20°C, the validity period will be determined by the long-duration stability study.

Art. 22. For products conserved at 2°C to 8°C and at -20°C, packed in semi-waterproof containers, the necessary information for evaluating the extent of water loss should be provided.

Section III
Of the Accelerated Stability Study

Art. 23. The tests for the accelerated stability study should be run at least at 0, 3 and 6 months, if product validity is greater than 12 (twelve) months.

Art. 24. Data obtained from previous years can be extrapolated for seasonal vaccines, with validity periods of up to 12 (twelve) months, and tests should be run concomitantly with vaccine use.

Art. 25. For products with validity periods of fewer than or equal to 12 (twelve) months, the company may contact the Biological Products Office - CPBIH to discuss when the tests for the accelerated stability study will be run and their frequency.

Section IV
Of the Long-duration Stability Study

Art. 26. For products with validity periods greater than 12 (twelve) months, tests for long-duration stability studies should be conducted at least every 3 (three) months during the first year of storage, every 6 (six) months during the second year and annually after that period.

Art. 27. For products with validity periods of up to 12 (twelve) months, tests should be run every 3 (three) months.

Art. 28. For products with validity periods of fewer than 12 (twelve) months, tests should be run every 3 (three) months.

Single paragraph. If the final month of validity is not included in this interval, all tests for the stability protocol should be conducted during the last month of validity.

Art. 29. Data obtained from previous years can be extrapolated for seasonal vaccines, with validity periods of up to 12 (twelve) months, and tests should be run concomitantly with vaccine use.

Section V
Of Stability Studies in Stress Conditions

Art. 30. Possible exposure of the product outside the recommended conservation care should be evaluated, such as high temperatures and/or freezing.

§ 1 – These occurrences should be evaluated in a stress study that demonstrates its impact on the quality of finished biological products.

I – the stress study should be conducted with at least 1 (one) lot of finished biological product.

§ 2 – If there are deviations in temperature during transportation and/or storage, stress studies should be presented and they will be analyzed for releasing the cargo.

I – in order demonstrate the maintenance of product characteristics, as stress study report should be presented with data obtained by the end of the product validity period.

§ 3 – The stress studies will not be obligatory documentation for the biological product registration request instruction.

Art. 31 – For products in liquid form, a study should be conducted to determine product freezing temperature if it is projected to be exposed to temperatures lower than 2°C.

Art. 32. The tests for a complete stability report should be conducted annually for the lots submitted to stress studies, as well as at the beginning and end of the study.

Art. 33. The provisions projected in Arts. 30 and 31 also apply to biological products already registered at ANVISA.

Section VI
Of the Follow-Up Stability Study

Art. 34. The follow-up stability study should be conducted with at least 1 (one) lot of finished biological product.

Art. 35. The tests for a complete stability report should be conducted annually for the lots submitted to follow-up stability studies, as well as at the beginning and end of the study.

Single paragraph. The follow-up stability study should be initiated at the end of the long-duration study.

Art. 36. The follow-up stability studies sent in the product's history of change should contain the period of time in which the active principle and the intermediate product, if applicable, remain stored prior to their use in the manufacturing of a finished biological product.

CHAPTER IV
OF CONDUCTING PHOTOSTABILITY STUDIES

Art. 37. Photostability studies should be conducted in accordance with the Photostability Studies Guide available on the ANVISA website.

§ 1 – Non-presentation of a photostability study for the active principle should be justified using scientific evidence that the active principle(s) did not suffer degradation in the presence of light.

§ 2 – The photostability study should be conducted on at least 1 (one) lot of finished biological product, if applicable.

Art. 38. The requests for changes in excipient, or in primary or secondary packaging, that modify the product's sensitivity profile to light should be accompanied by a new photostability study.

CHAPTER V
OF PRODUCT PURITY

Art. 39. For substances that cannot actually be characterized or products for which an analysis of purity cannot be conducted using analytical methodology, the company should propose and justify an alternative test procedure.

Art. 40. Potential degradation of products that may occur over time should be completely identified.

§ 1 – Degradation products should be quantified during the long-duration stability study to check for significant qualitative and/or quantitative changes in any of the stability studies (long-duration, accelerated or stress).

§ 2 – Acceptable degradation profiles should be stipulated based on the values for degradation products observed in the lots of active principle and finished biological product used in the pre-clinical and clinical studies, respectively.

Art. 41. Process impurities should also be duly qualified and, if necessary, quantified.

§ 1 – The impurities should be quantified if they offer health risks to users.

§ 2 – The lack of quantification of impurities should be duly justified.

CHAPTER VI
OF THE STABILITY STUDY REQUIREMENTS FOR REGISTRATION OF BIOLOGICAL PRODUCTS AND NEW BIOLOGICAL PRODUCTS

Section 1
Of the Active Principle, the Intermediate Product and the Product in Bulk

Art. 42. If the active principle, the intermediate product or the product in bulk are stored before formulation, that is, remain stored in a specific condition prior to the beginning of the next phase, the company should accelerated and long-duration stability data for at least 3 (three) lots.

§ 1 – If it is impossible to present stability results for 3 (three) lots at the moment of registration, the data for accelerated stability and long-duration may be presented for at least 1 (one) lot, accompanied by a justification and timetable for submission of results from other lots.

§ 2 – The packaging materials for storage used when conducting stability studies should be the same as those used in commercial lots.

Art. 43. The company should present accelerated and long-duration stability data for at least 6 (six) months if the active principle, the intermediate product or the product in bulk remain stored for a period equal to or greater than this.

§ 1 – Only the stability report for the long-duration study may be presented, with justification.

§ 2 – The company should proceed with the long-duration stability study, corresponding to the time the active principle, intermediate product or the product in bulk remain stored and attach the results of the concluded study to the product's history of change.

Art. 44. If the company does not submit the final report for long-duration stability studies in the product's history of change, the validity period shall be defined based on data already sent by the company.

Art. 45. In those cases in which the active principle remains stored for a period of fewer than 6 (six) months, the company should conduct the long-duration stability study corresponding to the time during which the active principle remains stored.

§ 1 – There should be at least 3 (three) sampling points of the active principle for each lot. These points should contain the initial and ending values for the tests and at least one point distributed in a uniform manner in relation to the time interval.

§ 2 – The documentation should contain the statistical tests that prove data fitness to the stipulated validity period.

Section II
Of the Finished Biological Product

Art. 46. The validity period for the finished biological product will be stipulated based only on long-duration studies.

Single paragraph. Accelerated stability studies will not be sufficient for determining the validity period.

Art. 47. Partial long-duration stability studies may be accepted for determining the validity period at the moment of registration.

§ 1 – The validity period granted the product will not exceed two times the period for which the partial long-duration study was conducted.

§ 2 – The report of the complete accelerated stability study should be presented together with the report for the partial long-duration study and be in compliance with what is stipulated in this Resolution.

Art. 48. If the company does not submit the final report for long-duration stability studies in the product's history of change, the validity period shall be defined based on data already sent by the company.

Art. 49. Stability studies on at least 3 (three) lots of the finished biological product should be submitted for ANVISA evaluation.

§ 1 – Sampling should be representative of the industrial scale.

§ 2 – We recommend that lots of finished products used in the stability study come from different lots of the active principle.

§ 3 – We recommend using active principles and intermediate products with different storage times for production of the final product, for evaluating the product's cumulative stability.

Art. 50. Evaluate the interaction of the primary packaging and the closing system with the product in the horizontal or inverted positions whenever necessary, and in the vertical position for at least 1 (one) lot of the finished biological product.

§ 1 – Stability data obtained from all types of primary and secondary packaging and closing systems used for the finished biological product should be submitted to ANVISA.

§ 2 – Evaluate the possible substances from primary packaging and/or closing system that may interact and/or contaminate the product.

§ 3 - The company should justify the non-quantification and/or determination of these products throughout the stability studies if it decides to not do so.

Section III
Of the Stability of the Product in Use or the Reconstituted or Diluted Product

Art. 51. If the product has any solvent/diluting agent in its presentation to be used in the reconstitution or dilution of the medication, the company should protocol the accelerated and long-duration stability study for the diluting agent.

Art. 52. Stability of the product in use, or the reconstituted or diluted product should be demonstrated in the specified conditions of use and for the maximum storage time described on the label, directions and/or cartridge.

Art. 53. The stability study for the product in use, or the reconstituted or diluted product, should be conducted on at least 2 (two) lots of the finished biological product.

Single paragraph. We recommend running the tests on at least one lot at the end of the validity period.

Art. 54. If the finished biological product is packed in a multi-dose package, send ANVISA the data on the closing system's capacity to resist repeated insertions and removals of needles, maintaining the strength, purity, sterility and quality unaltered for the period specified in the instructions for use, in the conditions recommended by the manufacturer.

CHAPTER VII
OF THE STABILITY STUDY REQUIREMENTS FOR POST-REGISTRATION CHANGES OF BIOLOGICAL PRODUCTS AND NEW BIOLOGICAL PRODUCTS

Section 1
Of the general conditions for stability studies for post-registration changes

Art. 55. All post-registration changes approved with partial stability study data should have their studies concluded in accordance with product validity and the results should be submitted in the product's history of change after concluding the study.

§ 1 – If the accelerated stability studies have not been presented in the registration request, complete long-duration stability studies should be presented for all post-registration change requests.

§ 2 – The results of stability studies presented in the product's history of change should be duly identified and related to the petition of origin.

Art. 56. In the case of deviations observed during the stability studies, ANVISA should be notified immediately and the company should adopt those measures applicable and request a reduction in the validity period, when necessary, in accordance with the study results.

Art. 57. All of the results of the stability studies submitted in partial form in requests for post-registration change should be concluded in accordance with the medication's validity period and should be submitted to ANVISA in the product's history of change following conclusion of the study.

Art. 58. For post-registration changes, 3 (three) lots of the active principle, the intermediate product and the product in bulk or the finished biological product should be evaluated in the stability study, as per the case.

Art. 59. In those cases in which such significant differences have been verified in the quality attributes that it is possible to determine that pre- and post-change products are not highly similar, and thus, not comparable, a new registration should be requested.

Section II
Of the Change in Excipient in the Diluting Agent

Art. 60. If the company alters the composition of the diluting agent, it should analyze the risk of this change for the finished biological product.

§ 1 – The risk analysis should be based on the function of changed constituents, their interaction with primary packaging and the active principle, as well as the impact of the change on reconstituted product quality, based on analytical methodology.

§ 2 – The documentation containing the risk analysis study for determining the impact of the change on the formula for the diluting agent should be sent to ANVISA.

§ 3 – The stability studies held before and after the post-registration change should be compared and be part of the risk analysis, aimed at evaluating whether the changes imply a change in the quality of the diluting agent.

§ 4 – Complete accelerated stability studies and long-duration stability studies conducted for at least half the diluting agent's validity period should be presented, as well as the reconstituted/diluted product stability study.

§ 5 - ANVISA will decide whether to conduct the complete long-duration stability study for approval of the change/inclusion, if it verifies that the changes represent a health risk and may interfere in product quality and safety.

Section III
Of Change in the Excipient in the Intermediate Product, in the Product in Bulk and/or in the Finished Product

Art. 61. When there is a change in excipient in the intermediate product, in the product in bulk and/or in the finished product, after concluding the long-duration stability study submitted for registration, the company will conduct a risk analysis of this change, considering the preservation of product quality and safety.

§ 1 – The risk analysis should be based on the function of changed constituents, their interaction with primary packaging and the impact of the change on final product quality, based on analytical methodology whenever possible.

§ 2 – The documentation containing the risk analysis study for determining the impact of the change on the formula should be sent to ANVISA.

§ 3 – The stability studies conducted before and after the post-registration change should be compared and be part of the risk analysis, aimed at evaluating whether the changes imply a change in product quality.

§ 4 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of 6 (six) months or more, the company should submit the complete accelerated study together with the information on the change in excipient, and the long-duration stability study conducted for a period half as long as the approved validity period.

§ 5 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of fewer than 6 (six) months, the company should submit the information on the change in excipient and the long-duration stability study corresponding to the maximum period for which the product is stored.

§ 6 – Complete accelerated stability studies and long-duration stability studies conducted for at least half the approved validity period should be submitted for the finished product.

§ 7 - ANVISA will decide whether to conduct the complete long-duration stability study for approval of the change, if it verifies that the changes represent a health risk and may interfere in product quality and safety.

§ 8 – There should be at least 3 (three) sampling points on the graphs.

Section IV
Of the Change in the Master and Work Bench for Biotechnological Products and Vaccines

Art. 62. The company should present accelerated and long-duration stability data for at least 6 (six) months if the active principle remains stored for a period equal to or greater than this.

Art. 63. In those cases in which the active principle remains stored for a period of fewer than 6 (six) months, the company should conduct the long-duration stability study corresponding to the time during which the active principle remains stored.

Single paragraph. There should be at least 3 (three) sampling points on the active principle graphs.

Art. 64. The company should present a complete accelerated stability study and long-duration stability study conducted for at least half the approved validity period should be submitted for the finished biological product produced from the new master bench.

Section V
Of the Change in Manufacturing Site for the Diluting Agent

Art. 65. If the manufacturer of the diluting agent is changed, the company should protocol the complete accelerated and long-duration stability studies for the diluting agent, as well as a new stability study for the reconstituted/diluted product.

Section VI
Of the Change in Lot Size for the Active Principle, the Intermediate Product, the Product in Bulk and the Finished Biological Product

Art. 66. When lot size is changed, the manufacturer should conduct a new accelerated and long-duration stability study with the first 3 (three) lots of the active principle, intermediate product, product in bulk and/or finished product.

§ 1 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of (six) months or more, the company should submit the complete accelerated study together with the information on the change in lot size, and the long-duration stability study conducted for a period at least half as long as the approved validity period.

§ 2 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of fewer than 6 (six) months, the company should submit the information on the change in lot size and the long-duration stability study corresponding to the maximum period for which the product is stored.

§ 3 – Complete accelerated stability studies and long-duration stability studies conducted for at least half the approved validity period should be submitted for the finished product.

§ 4 – There should be at least 3 (three) sampling points on the graphs.

Section VII
Of the Change Process for Production of the Active Principle, the Intermediate Product, the Product in Bulk and the Finished Biological Product

Art. 67. The company should conduct a risk analysis on the change in the manufacturing process for the active principle, the intermediate product, the product in bulk and/or the finished product.

§ 1 – The risk analysis should be based on the impact of the change in maintaining the quality, safety and effectiveness of the finished biological product.

§ 2 – If minor changes in the manufacturing process have no impact on product quality, the absence of stability studies should be justified.

Art. 68. The manufacturer should conduct a comparative analysis between the accelerated stability study performed before and after the change to determine the possibility of impacts in maintaining the quality of the finished biological product.

§ 1 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of (six) months or more, the company should submit the complete accelerated study together with the information on the change in the production process, and the long-duration stability study conducted for a period at least half as long as the approved validity period.

§ 2 - In those cases where the active principle, the intermediate product and/or the product in bulk remain stored for a period of fewer than 6 (six) months, the company should submit the information on the change in the production process and the long-duration stability study corresponding to the maximum period for which the product is stored.

§ 3 – Complete accelerated stability studies and long-duration stability studies conducted for at least half the approved validity period should be submitted for the finished product.

§ 4 – There should be at least 3 (three) sampling points on the graphs.

Section VIII
Of the Expansion of the Temperature Range for Product Conservation

Art. 69. Complete accelerated stability studies and long-duration stability studies and a long-duration stability study conducted for at least half the approved validity period should be presented for determining the new temperature range for conservation.

§ 1 – The validity period granted the product will not exceed two times the period for which the partial long-duration study was conducted.

§ 2 – The final results of long-duration stability studies should be attached to the product's history of change.

§ 3 – A stability study should be conducted for each pharmaceutical form, material and/or packing for the product.

Section IX
Of the Expansion of the Validity Period for the Active Principle, the Intermediate Product and the Product in Bulk

Art. 70. Only complete long-duration stability studies will be accepted for expanding the validity period for the active principle, the intermediate product and the product in bulk.

Art. 71. When a new validity period is determined for the active principle, the intermediate product and the product in bulk, based on the latest results from long-duration stability studies, there should be documentation proving the change in validity period will not impact the quality of the finished biological product.

Section X
Of the Expansion of the Validity Period and Conservation Care for the Finished Biological Product

Art. 72. Only complete long-duration stability studies will be accepted for expanding the validity period or changing the conservation care of the finished biological product.

Single paragraph. A stability study should be conducted for each pharmaceutical form, material and/or packing for the product.

Section XI
Of the Update of the Strain for Flu Vaccine Production

Art. 73. The data from the complete accelerated stability study should be submitted for the formulation to be used, as well as the partial data for the long-duration study.

Art. 74. The data from the complete long-duration study should be sent for the vaccine used in the previous period.

Section XII
Of the Exclusion of Product Conservation Care

Art. 75. Only complete long-duration stability studies will be accepted for the exclusion of product conservation care.

Single paragraph. A stability study should be conducted for each pharmaceutical form and/or packing material for the product.

Section XIII
Of the Inclusion of Primary Packing

Art. 76. The stability study submitted to ANVISA should include information on all material that comprises the primary packaging and the closing systems used, indicating which have contact with the product.

Art. 77. Complete accelerated stability studies and long-duration stability studies conducted for at least half the approved validity period should be submitted.

§ 1 - Evaluate the interaction of the primary packaging and the closing system with the product in the horizontal or inverted positions whenever necessary, and in the vertical position for at least 1 (one) lot of the finished biological product.

§ 2 – Evaluate the possible substances from primary packaging and/or closing system that may interact and/or contaminate the product.

Art. 78. If the finished biological product is packed in a multi-dose package, send ANVISA the data on the closing system’s capacity to resist repeated insertions and removals of needles, maintaining the strength, purity, sterility and quality unaltered for the maximum period in use, in the conditions recommended by the manufacturer.

Section XIV
Of the Inclusions/Change in Manufacturing Site for the Active Principle, the Intermediate Product, the Product in Bulk and the Finished Biological Product

Art. 79. The stability studies conducted by the new manufacturers shall be part of the risk analysis aimed at evaluating whether the new manufacturing conditions imply a change in product quality in its different phases.

§ 1 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of (six) months or more, the company should submit the complete accelerated study together with the information on the inclusion/change in manufacturing site, and the long-duration stability study conducted for a period at least half as long as the approved validity period.

§ 2 - In those cases where the active principle, the intermediate product and the product in bulk remain stored for a period of fewer than 6 (six) months, the company should submit the information on the change in lot size and the long-duration stability study corresponding to the maximum period for which the product is stored.

§ 3 – Complete accelerated stability studies and long-duration stability studies conducted for at least half the approved validity period should be submitted for the finished product.

§ 4 – There should be at least 3 (three) sampling points on the graphs.

Art. 80. ANVISA will decide whether to conduct the complete long-duration stability study for approval of the change/inclusion, if it verifies that the changes represent a health risk and may interfere in product quality and safety.

Section XV
Of the Inclusion of a New Commercial Presentation

Art. 81. The new commercial presentations will not require a new stability study if:

§ 1 – There is no change in the number of units, volume and/or mass per primary packaging of the finished biological product;

§ 2 – The dose is included in the interval between the smallest and biggest dose of the stability study already sent to ANVISA.

Art. 82. Complete accelerated stability studies and long-duration stability studies conducted for at least half the approved validity period for those cases that do not fit in art. 81 should be submitted.
Single paragraph. The validity period granted the product will not exceed two times the period for which the partial long-duration study was conducted.

Section XVI
Of the Inclusion of a New Concentration

Art. 83. For the inclusion of a new concentration, the company should conduct a complete accelerated stability study and a long-duration stability study.

Single paragraph. The validity period granted the product will not exceed two times the period for which the partial long-duration study was conducted.

Section XVII
Of the Inclusion of a New Pharmaceutical Form

Art. 84. An accelerated stability study and a long-duration stability study should be conducted for each pharmaceutical form.

Art. 85. Long-duration stability studies conducted for at least half the validity period for determining the validity period will be accepted at the moment of inclusion analysis in the following conditions:

§ 1 – The validity period granted the product will not exceed two times the period for which the partial long-duration study was conducted.

§ 2 – The report of the complete accelerated stability study should be presented together with the report for the partial long-duration study and be in compliance with what is stipulated in this Resolution.

CHAPTER VIII
OF THE FINAL AND TRANSITORY PROVISIONS

Art. 86. For imported products, the stability studies may be conducted abroad as long as they comply with the temperature and humidity parameters defined in this Resolution.

Art. 87. The provisions of this Resolution apply to the stability studies to be initiated starting November 1, 2011.

Art. 88. This Resolution takes effect on the date of its publication.

DIRCEU BRÁS APARECIDO BARBANO

ANNEX I

Conditions for conducting stability studies on the active principle, the intermediate product and the product in bulk

TEMPERATURE AND HUMIDITY P LONG-DURATION STUDY	TEMPERATURE AND HUMIDITY – ACCELERATED STUDY
25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	40 °C ± 2°C 75% RH ± 5% RH
2°C - 8°C	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH
-20°C	The temperature and humidity parameters will be defined by the manufacturer

ANNEX II

Conditions for conducting stability studies for the finished product

TEMPERATURE AND HUMIDITY P LONG-DURATION STUDY	TEMPERATURE AND HUMIDITY – ACCELERATED STUDY
25 °C ± 2 °C/60% RH ± 5% RH (only products where use is restricted to hospitals) or 30 °C ± 2 °C/75% RH ± 5% RH	40 °C ± 2°C 75% RH ± 5% RH
5°C ± 3°C	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH
-20°C	The temperature and humidity parameters

	will be defined by the manufacturer

ANNEX III

Conditions for conducting stability studies for the water-based products

TEMPERATURE AND HUMIDITY P LONG-DURATION STUDY	TEMPERATURE AND HUMIDITY – ACCELERATED STUDY
25 °C ± 2 °C/40% RH ± 5% RH (only products where use is restricted to hospitals) or 30 °C ± 2 °C/35% RH ± 5% RH	40°C ± 2°C and no more than 25% RH