

Agência Nacional de Vigilância Sanitária [National Health Surveillance Agency]

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Public Consultation no 22, of July 4th, 2008

D.O.U [Official Journal] of 05/06/2008

The Collegiate Board of Directors of the National Health Surveillance Agency, in the use of the attributions vested in it under Article 11, item IV of the ANVISA Regulation approved by Decree N° 3.029 dated 16 April 1999, c/c of item V and on §§ 1st and 3rd of the Article 54 of the Statute that was approved under the terms of the Annex 1 of the Administrative Rule no 354 of the ANVISA, of August 11th, 2006, which was republished in the Official Journal of August 21st, 2006, during meeting held on May 29th, 2008.

Adopts the following Public Consultation and I, the CEO, determine its publishing:

Article One. The period of 45 (forty-five) days is hereby started, from the date of the publication of this Public Consultation, for submission of reviews and suggestions regarding the RDC proposal for the publication of a GUIA PARA DETERMINAÇÃO DA EQUIVALÊNCIA FARMACÊUTICA E BIOEQUIVALÊNCIA DE MEDICAMENTOS SPRAYS E AEROSSÓIS NASAIS [Guidance for Pharmaceutical Equivalence and Bioequivalence of Nasal Sprays and Aerosols].

Article Two. Inform that the Resolution proposal shall be availed, in its totality, during the consultation period at the address <http://www.anvisa.gov.br/divulga/consulta/index.htm> and the suggestions must be forwarded, in writing, to the following address: Agência Nacional de Vigilância Sanitária/ Coordenação de Inspeção em Centros de Equivalência e Bioequivalência, **SIA, Trecho 5, Área Especial 57 - Brasília (DF) - CEP 71205-050**; Telephone: **(61) 3462-5562** or Fax: (61) 3462-5563; or to the e-mail: bioequivalencia@anvisa.gov.br.

Article Three. Upon the end of the period under the terms of the Article One, the National Health Surveillance Agency shall join other involved Bodies and Institutions and those who stated interest in the matter to indicate representatives for further discussions to consolidate a final text.

DIRCEU RAPOSO DE MELLO

ANNEX

RESOLUTION – RDC No

Determines publication of Guidance for Pharmaceutical Equivalence and Bioequivalence of Nasal Sprays and Aerosols

The Collegiate Board of Directors of the National Health Surveillance Agency, upon the competencies granted by the item IV of the Article 11 and the Article 35 of the ANVISA Rules, which was approved by the Decree no 3.029, of April 16, 1999, and considering the stipulations of the item V and the s §§ 1st and 3rd of the Article 54 of the Statute that was approved under the terms of the Annex 1 of the Administrative Rule no 354 of the ANVISA, of August 11th, 2006, which was republished in the Official Journal of August 21st, 2006, during meeting held on xxxx of xxxxx, 2008, and

considering the Article 12 and the Article 16 and subsequent of the Law 6,360, of September 23th, 1976, the § 10 of the Article 14 of the Decree no 79.094, of January 5th, 1977, as well as the item IX, of the Article Seven of the Law no 9.782, of January 26th, 1999;

considering the stipulations in the items 1.7 of the Resolution no 897 of May 29th, 2003 and 1.c of the Resolution no 1170 of April 19th, 2006;

considering the need to establish criteria to evaluate quality, efficacy and safety of nasal medications in sprays and aerosols for registration as generic and similar drugs;

considering this issue was submitted for the consideration of the Collegiate Board of Directors, which approved the matter on March 6, 2003;

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

Article One. Order the publication of Guidance for the Pharmaceutical Equivalence and the Bioequivalence of Nasal Sprays and Aerosols, which has been availed at ANVISA website by the Thematic Series;

Article Two. This Resolution shall be in effect on the date of its publication.

DIRCEU RAPOSO DE MELLO

THEMATIC SERIES
NATIONAL HEALTH SURVEILLANCE AGENCY

**Guidance for Pharmaceutical Equivalence and the Bioequivalence of
Nasal Sprays and Aerosols**

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National Health Surveillance Agency

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1. Introduction

The Law no 9787/99, which establishes the generic drug in Brazil, states that the bioequivalence is the demonstration of therapeutical equivalence between two drugs holding a comparable bioavailability that are tried under the same experimental design, thus being an indication of the absorption speed and extension of the drug in its dose form.

Since 2001, ANVISA has been publishing several Resolutions to establish criteria and requirements to conduct a bioequivalence Trial to register drugs that have been updated along the development of science.

The Resolution no 897/03, which deals with the exemption and the substitution of bioequivalence trials, determines that nasal spray medication be availed under the aqueous solution form. However, it is noted that several of these drugs are formulated as a suspensions.

These drugs, mainly, are used to treat allergic rhinitis. Considering the characteristics of these pharmaceutical forms, such as destination of the drug (local action), the low plasmatic levels of active ingredients (which encumbers the execution of a Bioequivalence Trial under the models established in the current legislation), the complexity and the cost of *in vitro* tests to evidence the Pharmaceutical Equivalence, the need to draw a proposal for execution of trials that would be based on scientific method, feasible (considering the technology that is available in Brazilian market) and which could comply with Good Practices for Bioequivalence/ Bioavailability was noted.

On 2006, a project with the objective of improve ANVISA's capability to evaluate Pharmaceutical Equivalence and Bioequivalence studies for nasal sprays and aerosols was added to the Cooperation Contract executed between ANVISA and OPAS [Pan-American Institution for Health].

Headed by Coordination of Inspection in Pharmaceutical Equivalence and Bioequivalence Centers (CIBIO), a working group composed of technicians of General Office of Drugs, representatives of universities, manufacturing companies, CROs and professionals was constituted to gather and evaluate data regarding the major aspects of efficacy, safety and quality of these products. Since then, a series of activities have been conducted, including meetings, conferences, technical visitations and studies follow up to subsidize the knowledge and the course of discussions in Brazil and around the world.

This Guidance represents the harmonization of thoughts and experiences, based on the scientific methodology that is currently available, of representatives that are involved in execution and evaluation of

in vitro and *in vivo* trials for nasal medications in academics, industrial and sanitary realms, Brazilian and international, consolidating a proposal to guide regulatory sector regarding the information to be submitted to ANVISA for registration of this type of drug.

The matter is complex and originates diverging opinions and this proposal does not represent the depletion of this discussion. The scientific advances, as well as new ideas will be welcomed, always, to contribute for the discussion of this matter, whose main objective is to offer safe, and efficient and quality products to population.

2. Objective

The objective of this document is to introduce a series of recommendations and requirements for the execution of Pharmaceutical Equivalence and Bioequivalence trials with nasal sprays and aerosols, listing the necessary essays, methodology and the data to be submitted to ANVISA to prove safety and efficacy of these drugs for registration as a generic and similar drug..

3. Pharmaceutical Equivalence of Nasal Sprays and Aerosols

The Pharmaceutical Equivalence consists in verifying if test drug (T) complies, integrally, with the specifications of the Pharmacopoeia and with the remaining performance tests as described in the Guidance, and if results obtained are equivalent to the results of reference drug (R). The batches must be submitted in parallel to the essays established in the monograph of the Brazilian Pharmacopoeia or remaining official publications, as per the current Resolutions and the referred Guidance. Standard Chemical Substances (SQR), which have been standardized by the Brazilian Pharmacopoeia, and other pharmacopoeia codes authorized by the current legislation, must be employed. Trials employing working standards, as long as the certification is evidenced, in absence of SQR, shall be admitted. The results obtained for test drug (T), shall be compared to the results of the reference drug (R), thus, determining existence or lack of Pharmaceutical Equivalence.

All the procedures for Pharmaceutical Equivalence, as well as the reporting, must follow the terms of the GUIA PARA REALIZAÇÃO DO ESTUDO E ELABORAÇÃO DO RELATÓRIO DE EQUIVALÊNCIA FARMACÊUTICA E PERFIL DE DISSOLUÇÃO [Guidance for Execution and Reporting of Pharmaceutical Equivalence Tests and Dissolution Profile] .

3.1 *Staff*

Trained and qualified analysts shall conduct the Pharmaceutical Equivalence of Nasal Sprays and Aerosols analysis.

Quality Assurance Management of lab must assure that staff received the proper training to perform these tests and to operate equipments. Whenever applicable, training regarding principles and theories related to techniques employed must be conducted and its efficacy must be evaluated. Only the analysts who are able to evidence competency, or who are properly supervised, might conduct the Pharmaceutical Equivalence essays. The continuous training must be monitored and capable of identifying improvement needs.

3.2 *Environment*

It is a typical lab for Pharmaceutical Equivalence analysis, constituted by the essays facilities (area of bench sample preparation and equipment).

Samples, standard reagents and reference materials must be properly stored to warrant their integrity and traceability.

The environment of lab must have enough room to allow that working areas be kept clean and organized. The space must be proportional to the volume of analysis conducted and to internal organization of lab.

3.3 *Equipments and Instruments*

All equipment and instruments employed must be installed according to manufacturer's recommendations, meeting calibration, maintenance and periodic cleaning recommendations as well as allowing evaluation and traceability of data generated.

3.4 *Pharmaceutical Equivalence Tests*

The drug products, in accordance with GUIA PARA REALIZAÇÃO DO ESTUDO E ELABORAÇÃO DO RELATÓRIO DE EQUIVALÊNCIA FARMACÊUTICA E PERFIL DE DISSOLUÇÃO [Guidance for Execution and Reporting of Pharmaceutical Equivalence Tests and Dissolution Profile] must

completely meet the Pharmacopoeia requirements of the individual monograph that is stated in Brazilian Pharmacopoeia. In case of any other authorized Pharmacopoeia be used, the requirements of monograph must be complemented with the essays that are described in General Methods of current Brazilian Pharmacopoeia, described for the pharmaceutical form studied.

In the absence of Pharmacopoeial method, the study must be undertaken using a method that has been validated by test drug product manufacturer and must be co-validated by the study executor lab, with the complementation of essays described in General Methods of current Brazilian Pharmacopoeia. The essays that are required to evidence Pharmaceutical Equivalence of these drugs are:

Table 1- Essays required for the Pharmaceutical Equivalence

Pharmaceutical Form	Essays
Nasal Sprays and Aerosols	<ul style="list-style-type: none"> i. General Essays of the Brazilian Pharmacopoeia ii. Uniformity of Delivered Dose; iii. Number of Actuations/Dose per Unity iv. Droplet/Particle Size Distribution by Laser Diffraction v. Prime and Reprime; vi. Spray Pattern;

3.4.1 Pharmacopoeia Tests

3.4.1.1 **Aspect:** A detailed description of test and reference drug products as to appearance (color), characteristic odor, viscosity, presence of particles to characterize each one of them. Description must follow Brazilian Pharmacopoeia;

3.4.1.2 **Average Volume:** Determination of nominal volume in liquid products with multiple doses is executed by content weight. Weightings are executed by a scale with proper sensitivity, duly calibrated. Analysis follows the methods of Brazilian Pharmacopoeia using the amount of flasks and the specification in accordance with stated volume. The average volume must be determined, only, for drugs whose volumes are stated on the label.

3.4.1.3 **pH:** Analysis of acidity or alkalinity of a solution. The pH is a characteristic of solution substances that is determined by the concentration of Hydrogen (H⁺). Follow official methodology and specification for each active ingredient;

3.4.1.4 **Identification:** Analysis must be capable of evidencing the identity of the active ingredient in samples of the test and the reference drug product. Follow official methodology and specification for

each active ingredient (retention time, thin layer chromatograph, characteristic reaction, etc);

3.4.1.5 **Assay:** Follow official methodology and specification of each active ingredient. In absence of an official Pharmacopeia monograph, assay must employ validated method provided by the requesting Company that must be co-validated by study executor lab. Proceed the analysis using part of the content of ten (10) different flasks, disposing the first actuations necessary for priming, whenever applicable.

3.4.1.6 **Related Substances:** Whenever applicable, in accordance with official methodology of each active ingredient.

3.4.1.7 **Microbiological Essays:** Follow the general methods of current Brazilian Pharmacopeia.

3.4.2 **Specific Tests:**

3.4.2.1. **Uniformity of Delivered Dose:** The determination of uniformity of delivered dose must be executed in accordance with the following description, taking into account the Pharmacopeia methodology available and assay method for the active ingredient. *Sample Proceedings:* To warrant reproducibility of collection of samples, the employment of mechanical actuation methods is recommended. Mechanical actuation proceedings must hold controls that are adequate for critical parameters such as actuation strength, speed, and time interval between actuations. Test must be conducted in unities that have been primed in accordance with the instructions of use. Test must be executed with the vertical, or close to the vertical positioning of flasks. The essay must be executed with the collection of the first delivered dose immediately after priming and the last labeled dose. For suspensions, the dose must be released in a proper recipient, which might allow the due transfer of the content. The analytical method for assay shall yield the determination of the quantity of active ingredient in each delivered dose and the data must be reported as percents of labeled dose. For solutions, dose can be gravimetrically determined from the weight of the delivered dose, the concentration, and the density of tested solution. *Analysis of the Uniformity of Delivered-Dose:* Shall be conducted in 10 flasks, one collection in the beginning and another at the end of the doses. The test shall comply if no more than 2 of the 20 measured doses are outside the interval of from 80% to 120% of labeled dose; if none of the doses are outside the interval from 75% to 125% of labeled dose, and if the mean of the initial and the final actuations is between 85% and 115% of labeled dose. Should 3 of the 6 analyzed doses be outside the interval from 80% to 120% and the mean of the initial actuations and the average of the final actuations be between 85% and 115% of labeled dose, the analysis , 20 additional byls might are conducted. The test shall comply with the specifications if no more than 6 of the 60 doses are outside the interval of from 80% to 120% of labeled dose; none is outside the interval of from 75% to 125% of labeled dose, and if the mean of the 30 initial actuations and the mean of the 30 final actuations

are between from 85% to 115% of labeled dose.

3.4.2.2 Number of Actuations/Dose per Unity: Proceed the analysis in three unities to determine the number of actuation/dose per unity. The number of doses generated by each of the unities tested must be counted and related to the declared by manufacturer. Actuations must be conducted in accordance with procedure described in label. Results must be evaluated by the mean of three tested unities and it must not be smaller than the labeled number of doses.

3.4.2.3 **Droplet/Particles Size Distribution:** Distribution and the size of the droplets/particles is an important property of sprays and aerosols and influences nasal deposition, thus, needs to be well characterized. Laser diffraction is a non-aerodynamic optical method for measuring droplets/particles, and assessing their geometrical size following actuation. Laser diffraction equipment that is available provides *obscuration data* (optical concentration), *transmittance percent (%T)* and *droplets distribution* (D_{10} , D_{50} , and D_{90}). In addition, Span ($D_{90} - D_{10}/D_{50}$) must be obtained from these data. To conduct the essay, is recommended the compliance with the equipment's manufacturing instructions regarding to obscuration and transmittance percent. Further, actuation parameters (strength, speed and interval between actuations), must be established and controlled. Plumes generated by actuation of this kind of drug products can be characterized in three stages: formation, complete development and dissipation. Assessments must be executed during plume's complete development stage. All information generated, as well as SOP to conduct analysis must be printed and submitted. Operational parameters and conditions that were established for equipment, also, must be submitted. *Analysis of distribution of size of particle:* Essay must be conducted with three (3) flasks for test drug and three for reference drug. Results of assessments must be reported based on the volume (mass) and must be obtained from the plume's complete development stage that were generated in the onset of the doses, following the preparation, and the final doses of each flask. In addition, data of two different distances from the laser and the orifice of flasks must be evaluated. It is recommended a distance of 2 to 7 cm between the laser and the orifice, and that they hold a detachment of 3 cm, or more, between them. Comparison must be carried considering droplet/particle distribution data of each drug and Spam.

3.4.2.4 **Prime and Reprime:** For some reference drugs, it's necessary some procedures for preparing the product for initial usage (prime) or for one or more periods during which the medications is not used (reprime). Prime and Reprime data of drugs will warrant the release of labeled dose in accordance with the drug manufacturer's recommendations for use.

The test products' recommendations for use must be clear and complete about priming and repriming procedures and tests must be conducted strictly following these procedures. Essay must be conducted considering periods that are described in label and after storage in multiple orientations (vertical,

horizontal and inverted), unless there is a specific determination established by the drug manufacturer. *Analysis of the Charge and Recharging data:* Essay must be conducted using 10 flasks of test drug and 10 of reference drug. For suspensions, test must employ the methodology established in available Pharmacopoeia, or a validated methodology in the absence of a Pharmacopoeial methodology to determine the delivered dose. For solutions, must be determined the relative mass of each actuation per flask by differences in weight before and after actuation. The delivered dose must be between 85% and 115% in relation to the labeled and a maximum of 6% of relative standard deviation.

3.4.2.5. **Spray Pattern:** Characterizes the form and the density of the plume generated by both test and reference spray, using non-impact mechanisms, with visualization by laser light or impact mechanism system, using a proper target that must allow the visualization of the generated spray. Spray Pattern can be characterized and quantified by manual or automatic image, as long as validated. Data and documents generated must be submitted, as well as essay execution SOP. *Spray Pattern Analysis:* This analysis must be executed in 3 (three) unities of test and reference drug, using the same impact mechanisms, executing actuation on a proper target. Simple actuation must be executed at beginning dose (following the preparation) in two distances defined between orifice of flask and the impact surface, of at least 3 cm, within 3 to 7 cm variation. Must be determined center of mass (COM), maximum Diameter (Dmax) and minimum Diameter (Dmin), traced from this center. The results must be expressed by the ratio Dmax/Dmin, with the determination of mean of three actuations.

4. Pharmacokinetics Studies for Nasal Sprays and Aerosols

Relative bioavailability/bioequivalence (BR/BE) studies for local action drugs, such as nasal sprays and aerosols, present a pharmacokinetics/therapeutical effect that is different from the conventional BR/BE (drugs for systemic action) as in this instance, drugs reach site of action before they are absorbed by systemic circulation. The droplets/particles are deposited on mucous and drugs, then, are absorbed and might yield systemic effects even though the plasma concentrations do not portray its therapeutical capability. Drugs that are administrated by nasal route display a characteristic pharmacokinetic behavior, which is absorption by two distinct routes: nasal mucous and gastrointestinal tract, since there is a swallowing portion of the drug. Therefore, plasmatic concentrations of drugs that are administered by nasal route result from local and oral absorption. Though the objective of these drugs is local action, consequences of systemic absorption, such as suppression of the hypothalamus-pituitary-adrenal (HPA) axis, must be taken into consideration.

For drugs that are administered by nasal route, bioavailability is related to a series of factors: apparatus by which the drug will be delivered, deposition of droplets/particles on the respiratory tract, the amount

deposited, size of the droplets, their dissolution (for suspensions) and speed of clearance by the respiratory tract (mucocilliary clearance).

Analytical methods that are currently available for quantification of drugs in biological samples, specially LC-MS/MS methods, allow quantification of glucocorticosteroids following nasal administration with pharmacokinetics application. Thus, it is possible to evaluate bioequivalence of these drugs using the same criteria established for the oral route drugs (Guidance for Evidences of Relative Bioavailability/Bioequivalence of Drugs) with some observations, which will be discussed as follows.

4.1 Considerations on Clinical Phase:

Clinical phase of Relative Bioavailability/Bioequivalence of Drugs administered by nasal route is the phase that differs the most from studies with drugs that are administered by oral route, mainly about care of drug administration, administered dose, screening of volunteers and execution of study.

Study must be conducted, preferably, with one single dosage, and multiple dose studies must be justified in protocol. Considering that drugs administered by nasal route reach low plasmatic concentrations, doses administered can be equal, or higher, than therapeutic doses, as long as safety of volunteers is warranted. The choice of the dose must be justified in the protocol and the study shall not be started before protocol is authorized by Independent Ethics Committee. Schedule of collection of samples must warrant proper characterization of plasmatic profile of drugs, however it must be considerate, besides half-life of elimination, the capability of analytical method to quantify drug by proposed period.

4.1.1 Inclusion and exclusion criteria:

Inclusion and exclusion criteria of Relative Bioavailability/Bioequivalence of nasal sprays and aerosols are equal to criteria of drugs administered by oral route added by an exam that evidences that the respiratory capability is within normal criteria. Study must be conducted with healthy volunteers, of both genders, whose weights are within the normal range.

Volunteers, in order to be included in these studies, must be submitted in a clinical evaluation, and no respiratory disease must be found, which includes allergic rhinitis, nasal septal deviation, and adenoid, as they might alter deposition of drug into nasal mucous. Before beginning clinical phase, volunteers must receive training regarding administration of drugs. There must be an application of placebo with the same apparatus to evaluate tolerance of volunteer to receipt of drug without reactions, which, generally, result in sneezing. Should the volunteer display any intolerance to the administration, he/she ought not to be included in the trial.

Exclusion criteria are equal to those for oral route drug studies, highlighting importance of non-inclusion of smokers, or former smokers who have abandoned the habit just recently.

Another exclusion criteria used for nasal sprays and aerosols is the occurrence of a sneeze two hours after administration of the drug.

4.1.2 Administration Care

To assure maximum absorption and minimize intra and inter-subject variation some precautions must be implemented during administration of these drugs:

- Each volunteer must receive drug by an individual flask;
- All volunteers and staff must wear clean area clothing, including caps, masks, and gloves;
- Before each application, the device must be tested by trained staff and execution of about 5 actuations is recommended, outside the building, on the day prior to the testing day;
- Flasks must be weighted after 5 actuations and, again, after administration in the volunteers. The weight of flasks after administration is an exclusion criteria, and the mean of the values. The weight of each flask must be calculated and must fall within two standard deviations.
- Volunteers must be previously trained to use the apparatus that will receive the formulation to inhale properly;
- Before nasal administration (1 minute), volunteers must blow their noses;
- During nasal application, one of the nostrils must be obstructed while administration is executed in the other nostril. It is recommended that time elapsed between first and last actuation does not exceed 1 minute;
- After last application, volunteers must receive a 200 ml glass of water to conduct particles of drug that might have remained in oral cavity to gastrointestinal tract;
- Drug must be administered in a room, and volunteers must be led to another room where blood samples will be drawn, minimizing the cross-contamination. Following administration, volunteer must leave the room, wash his/her hands and face and go to collection room.
- Air-conditioning of room where drugs will be administered must be off during all the procedure;
- Air-conditioning of collection room must be off for, at least, two hours after administration;
- Blood samples must be processed (centrifuged) in a room that is separate from administration and collection rooms;

4.2 Considerations on Analytical Phase

In accordance with descriptions of literature there are no analytical difficulties in quantification of drugs following administration by the nasal route, however, there is requirement for an equipment with a sensitivity that is compatible with these trials. Analytical phase must comply with the requirements of Guidance for Evidences of Relative Bioavailability/Bioequivalence of Drugs.

4.3 Considerations on the Pharmacokinetics and Statistical Phases

Relative Bioavailability/Bioequivalence studies must be planned in accordance with Guidance for the Planning and Execution of the Statistical Phase for Evidences of Relative Bioavailability/Bioequivalence Trials of Drugs.

Initially, all volunteers who had all samples collected must be included in analysis.

As a result of the low bioavailability of some drugs by nasal administration, it might not be possible to determine elimination half-life ($t_{1/2}$), constant of elimination (K_{el}) and the area under the curve of plasmatic concentration versus time in the interval from 0 to infinity ($AUC_{0-\infty}$) for all volunteers, which might not result in exclusion of volunteer from study. In this case, it will not be required that the values AUC_{0-t} be greater than 80% of the $AUC_{0-\infty}$. Volunteers whose quantification of drug in biological samples were above limit of quantification in less than 4 collection points in one of the treatments, and to whom the quantification of samples displays sufficiently expressive issues that impair comparison between test and reference performance must be excluded from the study. Still, all values of C_{max} that were above the limit of quantification, even for the volunteers to whom the AUC was not possible to calculated in some of the treatments, shall be included in statistical analysis of the C_{max} . Exclusions must be documented and justified in Final Report.

Bioequivalence criteria must follow stipulated criteria in Guidance for Evidences of Relative Bioavailability/Bioequivalence of Drugs, i.e., the mean bioequivalence conclusion is reached between the two formulations when 90% confidence interval of the ratio of AUC_{0-t} (in regards to the extension of absorption) and C_{max} (in regard to absorption speed) geometrical means are between 0,8 and 1,25. Other previously established limits of IC 90% for the C_{max} might be accepted by a scientific justification and must be previously established in protocol.

5. Pharmacodynamic Studies for Nasal Sprays and Aerosols.

For suspension nasal sprays and aerosols, whose plasmatic concentration of the active principle is very low and thus the execution a Pharmacokinetic study is not possible, a comparative Pharmacodynamic study might be executed using the endpoints that allow the evaluation of the relation between dose/response of each drug and which yield data that might be used to determine of the bioequivalence between them.

Pharmacodynamic studies must comply with all requirements and recommendations that were established by Good Practices of Bioavailability/Bioequivalence and it must allow traceability of all the generated data.

It is recommended that design and evaluation parameters of the study be previously discussed and submitted to ANVISA as a protocol.

Pharmacodynamic studies must comply with the following criteria:

5.1 *Validation*

Data that warrants applicability of method to obtain pharmacodynamic parameters used to evaluate bioequivalence must be submitted. Thus, results of the following tests must be submitted: studied pharmacodynamic response specificity, precision, accuracy and linearity.

5.2 *Positive correlation:*

Linear association measured between two variables. Correlation yielded values are between -1 and 1. The closer they are from the extremes (-1 or 1) the stronger is the linear association between the studied variables: closer to -1 implies an inverse correlation (or negative), i.e., the more one variable increases its magnitude the more the other is reduced; closer to 1 determines a direct correlation (or positive) i.e., the more one variable increases its magnitude the more the other increases, too.

5.3 *Robustness or Resistance*

Quality of an estimator in not suffering influence considering distortions encountered in a data bank (outliers, strong distribution asymmetry, etc). The statistical objective is extract valid inferences from a set of data. In addition to considering the data itself, any analysis is based on some hypothesis or assumptions regarding study situation. These assumptions are not real, if we consider the strict sense of term, they are rationalizations or simplifications of reality as a result of lack of knowledge of studied

phenomenon or as a necessity to “simplify” the phenomenon and yield application of available mathematical and computer tools. For that reason, stability of statistical procedures in general must be studied (and specifically estimation techniques) in presence of deviations from hypothesis which they are based and use techniques that are not very sensitive to these deviations. Such techniques are named resistant or robust.

5.4 Reproducibility

Represents grade of association or of agreement between measures done by different methods or significant non-difference between two methods. For example: in experiments for bioequivalence tests is the warranty that the reference drug is bioequivalent to the generic drug.

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