COLLEGIATE BOARD RESOLUTION - RDC NO. 742 OF 10 AUGUST 2022

Provides for the criteria to conduct relative bioavailability/ bioequivalence (BA/BE) studies and pharmacokinetic studies.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and item VI, paragraph 1 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Resolution, as decided upon in a meeting held on 9 August 2022, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and Scope

Article 1. This Resolution establishes the criteria to conduct relative bioavailability/ bioequivalence (BA/BE) studies and pharmacokinetic studies to ensure quality, safety, and efficacy of generic, similar, new, and innovative medicinal products and biological products.

Article 2. This Resolution covers the relative bioavailability/ bioequivalence (BA/BE) studies and pharmacokinetic studies that make up the consent dossiers in clinical research, marketing authorization or post-marketing authorization of generic, similar, new, and innovative medicinal products and biological products.

Paragraph 1. This Resolution applies to BA/BE studies that make up the marketing authorization dossiers of medicinal products when such studies are used as the main evidence to confirm the safety and efficacy of the medicinal product.

Paragraph 2. Additional evidence, new studies, or evaluation of parameters different from those described in this Resolution may be requested at any time.

Section II

Definitions

Article 3. For the purposes of this Resolution, the following definitions are applicable:

I – analyte: a specific chemical compound to be measured in a biological matrix;

II – bioavailability (BA): speed and extent of absorption of an active ingredient, from a pharmaceutical form, from its concentration/ time curve in the systemic circulation or its excretion in urine, measured based on the peak of exposure and the magnitude of exposure, or partial exposure;

III – relative bioavailability (RBA): comparison of the bioavailability of two products under the same experimental design;

IV – bioequivalence (BE): proof of equivalent bioavailability between products, when studied under the same experimental design;

V – raw data: set of values, data, or occurrences in their original state, without any alteration or treatment;

VI – study dossier: set of documents that present all data necessary to prove BE between two medicinal products;

VII – pharmaceutical equivalents: medicinal products that have the same dosage form, the same administration route, and the same quantity of the same active substance, that is, the same salt or ester of the therapeutic molecule, which may or may not contain identical excipients, provided they are well established for the intended function. They must comply with the same requirements of the individual monograph of the Brazilian Pharmacopoeia, preferably, or with those of other official compendia, specific norms or regulations approved/ endorsed by Anvisa or, in their absence, with other quality and performance standards. Modified-release dosage forms that require a reservoir or excess may or may not contain the same quantity of the active substance, provided they release identical quantities of the same active substance in the same dosage interval;

VIII – pharmaceutical equivalence study: set of physicochemical and, when applicable, microbiological and biological assays, which prove that two medicinal products are pharmaceutical equivalents;

IX – pharmacodynamic studies: studies that correlate the administration of a medicinal product to a measurable effect;

X – adverse event (AE): any unfavorable medical occurrence in a patient or clinical research participant to which medication has been administered, without necessarily having a causal relation with the treatment, and it may be any unfavorable and unintentional sign, symptom, or disease temporarily associated with the use of the medicinal product;

XI – active pharmaceutical ingredient (API): any substance introduced in the formulation of a dosage form that, when administered to a patient, acts as an active ingredient, and it can exert pharmacological activity or other direct effect in the diagnosis, cure, treatment, or prevention of a disease, and may also affect the structure and functioning of the human organism;

XII – comparator medicinal product: a medicinal product with which the test product will be compared;

XIII – narrow therapeutic index medicinal product: a medicinal product with a narrow safety margin, having a therapeutic concentration close to the toxic concentration;

XIV – reference medicinal product: an innovative product granted marketing authorization by ANVISA and commercialized in the country, the efficacy, safety, and quality of which were scientifically proven at the time of marketing authorization;

XV – test medicinal product: a medicinal product submitted to the BA/BE study or pharmacokinetic study of biological products that is compared to a comparator medicinal product;

XVI – research participant: an individual who, in an informed and voluntary manner, or with the clarification and authorization of his/ her legal guardian, consents to participate in the study;

XVII – study protocol: a document describing the objective(s), design, methodology, statistical considerations, and organization of a trial;

XVIII – term of free and informed consent (TFIC): a document in which the free and informed consent of the participant and/ or his/ her legal guardian is explained, in writing, and it must contain all the necessary information, in clear and objective language, easy to understand, for the most complete clarification of the research in which one proposes to participate; and

XIX – pharmacotechnical unit: a unit fraction of the medicinal product, corresponding to a vial, an ampoule, a pre-filled syringe, a flaconette, a sachet, an envelope, a tablet, a capsule, a vaginal egg, a pill, a transdermal patch, a suppository, or other packaging or dosage form permitted by specific legislation.

CHAPTER II

STUDY DOSSIER

Article 4. A summary of all BA/BE studies that have been performed for the same test medicinal product must be submitted as part of the study dossier, except for pilot studies carried out for exploratory purposes, according to the communication model of other studies carried out with the test medicinal product, available on Anvisa Electronic Portal, indicating at least the following:

I – the purpose of the studies;

II – the test medicinal products and comparators used;

III – the batches of medicinal products;

IV – the designs adopted; and

V – the results obtained.

Paragraph 1. The different batches of this medicinal product are understood as the same test medicinal product, including those that were produced with minor, moderate, or major alterations, as defined in Collegiate Board Resolution – RDC No. 73 of 7 April 2016, or another regulation that may succeed it.

Paragraph 2. The complete report of the studies provided for in the caption of this article may be requested at any time.

Paragraph 3. In case the same test medicinal product shows studies with different conclusions, a justification must be submitted for the acceptance of one result to the detriment of the other.

CHAPTER III

MEDICINAL PRODUCTS UNDER STUDY

Article 5. Prior to the beginning of the BA/BE study, the test and comparator medicinal products must be analyzed in accordance with Collegiate Board Resolution – RDC No. 31 of 11 August 2010, or any other regulation that may succeed it.

Paragraph 1. The difference in medication content between the test and comparator medicinal products, when they have the same concentration, must not exceed 5.00% (five percent).

Paragraph 2. When the pharmaceutical equivalence study is not applicable, quality control reports must be presented for each of the medicinal products used in the study.

Article 6. For medicinal products classified as generic or similar, the BA/BE study must be conducted with the same batch used in the pharmaceutical equivalence study.

Sole paragraph. If it is not possible to use the same batch, a justification for conducting the studies with different batches must be presented.

Article 7. To carry out the pharmaceutical equivalence and BA/BE tests, the comparator medicinal product must be purchased in Brazilian territory.

Sole paragraph. The provisions in the caption of this article do not apply to cases of import of comparator medicinal product unavailable in the Brazilian market, in accordance with Collegiate Board Resolution – RDC No. 35 of 15 January 15, or any other regulation that may succeed it.

CHAPTER IV

CLINICAL STAGE OF RELATIVE BIOAVAILABILITY/ BIOEQUIVALENCE (BA/BE) STUDIES

Section I

BA/BE Study Research Participants

Article 8. The BA/BE study must be conducted with healthy research participants.

Sole paragraph. A rationale for conducting the study with patients may be presented.

Article 9. The ethical principles, determined in Brazilian regulations and international multilateral agreements accepted by Brazil, must be respected.

Paragraph 1. The study protocol and the informed consent must be approved by a Research Ethics Committee (REC) or an institution with an equivalent function, prior to the admission of research participants.

Paragraph 2. The procedures with each research participant of the study may only be started after obtaining the free consent of the research participant or his/ her legal representative.

Article 10. The gender of research participants must be representative of the population indicated in the medicinal product package insert.

Sole paragraph. For toxicity reasons, a justification for conducting the study with only part of the population indicated in the package insert may be presented.

Article 11. Regarding the characteristics of the research participants, the following actions are necessary:

I – recruit research participants aged 18 or over and able to provide their free and informed consent;

II – have a Body Mass Index (BMI) between 18.5 and 30 kg/m² (inclusive); and

III – avoid smokers or individuals with a history of alcohol or drug abuse.

Sole paragraph. In the case of studies that require research participants with characteristics different from those mentioned above, their inclusion must be justified.

Article 12. Pregnant or lactating women should not participate in BA/BE studies.

Sole paragraph. When applicable, contraceptive methods should be prescribed and/or definitively sterilized participants should be selected.

Article 13. Research participants must undergo a clinical evaluation before the start of the study and after its completion.

Paragraph 1. The clinical evaluation must include medical history, physical examination, twelve-lead electrocardiogram (ECG), and laboratory evaluations including serology, hematology, biochemistry, and urinalysis.

Paragraph 2. Depending on the medicinal product, other clinical evaluations may be necessary before starting the study.

Paragraph 3. It is recommended to carry out the following laboratory tests: complete blood count; urea; creatinine; alkaline phosphatase; blood glucose; direct, indirect, and total bilirubin; total proteins; albumin; oxaloacetic and pyruvic transaminases (GOT and GPT); uric acid; total cholesterol; triglycerides; type I urine (routine urine); Beta HCG (for women); serology for hepatitis B, C, and HIV.

Paragraph 4. The serological tests do not need to be repeated in post-study.

Article 14. The design of the protocol and the conduction of the study must consider the warnings, precautions, contraindications, drug interactions, expected adverse events, and other information included in the package insert of the comparator medicinal product.

Paragraph 1. The studies must have specific monitoring for potential adverse events according to the medicine and, whenever necessary, must include additional procedures to monitor the participants, with an emphasis on safety.

Paragraph 2. Every adverse event must be evaluated in light of intensity (mild, moderate, or intense/ severe), severity (serious or not serious), causality (expected or unexpected), relationship with the study medicinal product (unrelated, unlikely, possible, probable, or related), course (recovered, recovering, unrecovered, fatal, or unknown), and intervention (pharmacological, clinical follow-up, repeat examination, hospitalization, or referral).

Article 15. An adverse event registration form, listing the procedures adopted to control or treat them, must be completed.

Article 16. When using medications other than the purpose of the study, medicinal products capable of interfering with the pharmacokinetics of the API under study, which interfere with its quantification in the analytical stage or that may be used as an internal standard, should be avoided.

Article 17. Phenotyping and genotyping tests may be considered in parallel-designed studies with medicinal products that have phenotype-linked metabolism, allowing slow and fast metabolizers to be distributed between the two groups of participants.

Sole paragraph. Phenotyping and genotyping may also be adopted for safety reasons for the research participant.

Section II

Medicinal products the BA/BE studies of which are to be conducted in patients

Article 18. Medicinal products with a significant risk to the safety of research participants may be tested in patients belonging to the target population of the study medicinal product and who are being treated for a pathology the comparator medicinal product is indicated for, according to its package insert.

Sole paragraph. Only patients who are stable in relation to the pathology should be included in the study.

Article 19. Preferably, patients on a monotherapy regimen should be included in the studies.

Sole paragraph. In the case of inclusion of patients who are undergoing polytherapy, co-medications must be present in all periods.

Article 20. In the case of participation of patients with different therapeutic dosage regimens, pharmacotechnical units of the same concentration must be administered.

Paragraph 1. If the number of pharmacotechnical units to be administered is incompatible with the dosage to be used, the patient should not be included in the study.

Paragraph 2. The statistical analysis to be performed must include all possible sources of variation that may interfere in the response variable, which includes the (inter patient) dosage, if it is necessary to use different dosage levels.

Article 21. The studies to be performed must consider an experimental design appropriate to their objectives, and the dosage to be administered to the same patient is always the same, and dosage normalization is not allowed.

Sole paragraph. In situations where the use of a parallel design is necessary, this should be done with a balance of patients in the test and comparator groups, considering the stage and type of pathology, as well as the treatment history and dosage regimen.

Article 22. The study should be conducted in a single dosage, however, in cases where such a dosage schedule is not feasible in patients, the study may be conducted with multiple dosages.

Paragraph 1. The therapeutic regimen (dosage) of patients must not be altered for the purpose of BA/BE studies.

Paragraph 2. In studies with multiple dosages, the start time of collections must be the same in the different periods, and the obtention of the equilibrium status must be ensured before sample collection.

Section III

Medication administration method

Subsection I

Conventional release medicinal products

Article 23. Medicinal products must be administered to research participants according to the route and method of administration described in the package insert of the comparator medicinal product, in a standardized way for all participants.

Article 24. The administration of medicinal products in a fasting period or in the presence of food will depend on the formulation and administration guidelines described in the package insert of the comparator medicinal product. Thus, the following rationale must be applied:

I – for conventional release oral dosage forms, the pharmaceutical of which do not have absorption influenced by the presence of food, the administration of the medicinal product must be carried out on an empty stomach, except when the package insert of the comparator medicinal product restricts its use with food, in which case the study must be performed with food;

II – for conventional release oral dosage forms, the pharmaceutical of which have absorption influenced by the presence of food, resulting in clinically significant alterations, the choice of administration form during the study will depend on the following factors:

a) when the exclusive use indication is administration under fasting conditions, a fasting study should be conducted;

b) if the exclusive use indication is administration with food, a study with food must be conducted; and

c) if the use indication allows for administration on an empty stomach or with food, or if there is no clear indication in the package insert, two studies must be carried out, one under fasting conditions and one with food.

III – for formulations involving specific production technologies, it may be necessary to present the study under fasting conditions and with food;

IV – for some medicines, where a high pH may cause a difference in bioavailability, considering distinct formulations, it may be necessary to carry out an additional study with the previous administration of proton pump inhibitors.

Sole paragraph. The information referred to in items I, II, III, and IV are compiled in a specific regulation and, if the medicinal product is not on the list, a prior consultation with Anvisa must be carried out, via Anvisa's service channels, to verify the conduction of the study under fasting conditions and/ or with food.

Article 25. For studies conducted under fasting conditions, a fasting period of at least eight hours before and four hours after medicine administration should be considered.

Article 26. For studies conducted with food, the composition of the meal must meet what is described in the package insert of the comparator medicinal product.

Paragraph 1. If there is no indication in the package insert regarding the composition of the meal, a high-fat, high-calorie diet must be offered, which causes significant effects on the gastrointestinal tract and, consequently, on the medicine bioavailability.

Paragraph 2. If the medicine administration time in relation to feeding time is not defined in the package insert, food must be offered thirty minutes before medicine administration, after a fasting period of at least eight hours.

Article 27. For multiple-dosage studies, with medicines that must be administered under fasting conditions, a minimum period of two hours before each administration should be considered.

Subsection II

Modified release products

Article 28. BE studies for extended-release oral dosage forms should be conducted under fasting conditions and with food.

Sole paragraph. For medicinal products that present a safety risk to research participants in one of the situations, justifications for conducting the study under a single condition may be presented.

Article 29. For delayed-release oral dosage forms with gastro-resistant coating, a study should be conducted under fasting conditions or with food, as described in the package insert of the comparator medicinal product.

Sole paragraph. If the package insert allows both forms of administration, under fasting conditions and with food, a study must be conducted in each situation.

Article 30. For extended-release formulations, in addition to the primary parameters to determine bioequivalence (AUC_{0-t} and C_{max}), the partial AUC parameter must be considered to calculate the area from time zero to half of the dosage interval (initial partial AUC) and from this until the last collection time (final partial AUC).

Sole paragraph. The provisions in the caption of this article apply exclusively to medicinal products that intend to be interchangeable in relation to a comparator.

Section IV

Design of the pharmacokinetic study

Article 31. The BA/BE study design should be randomized and crossover, and research participants should receive the test and comparator medicinal products in separate periods, in a single-dosage regimen.

Paragraph 1. The adoption of a parallel design, replacing the crossover one, may be performed for medicinal products that have a long half-life, provided that a standardization of the two groups of research participants is carried out, in order to minimize variability.

Paragraph 2. Multiple dosage studies may only be adopted when justified.

Subsection I

Analyte quantification

Article 32. The quantification of an unaltered medicinal product or its metabolite must follow the recommendations described in a specific regulation.

Paragraph 1. If the medicinal product is not on the list, a prior consultation with Anvisa must be carried out, via Anvisa's service channels, to verify the quantification of the analyte or its metabolite.

Paragraph 2. The analytes to be quantified must be previously defined in the study protocol, as well as which analytes will be evaluated by statistical methods, and which ones will determine the study result.

Article 33. The quantification of the analyte must be done from a biological matrix in blood, plasma or serum.

Paragraph 1. The quantification of the analyte in other biological matrices (for example, urine, feces, aqueous humor) may be accepted, provided it is not possible to quantify the analyte in the systemic circulation.

Paragraph 2. When the quantification of the analytes is carried out in urine, evidence must be presented that the urinary excretion will reflect systemic exposure.

Subsection II

Collection schedule

Article 34. The collection schedule must allow the characterization of the pharmacokinetic profile of the analyte under study and must be established based on the following factors:

I – the schedule must include the pre-dosage collection and extend for a period equal to or longer than three times the elimination half-life of the medicinal product or metabolite;

II – collection times must be provided for the adequate characterization of the absorption stage;

III – collection times in C_{max} region must be foreseen for the characterization of this parameter;

IV – the elimination stage must be evidenced with at least three collection points for the correct extraction of pharmacokinetic parameters; and

V – in the case of endogenous substances, at least three collections must be carried out to characterize the basal level of each research participant, in all periods of the study.

Paragraph 1. In the case of conventional release formulations, containing medicines that have an elimination half-life longer than 24 hours, a collection schedule of at least 72 hours must be used, with determination of the area under the truncated curve, or a parallel study.

Paragraph 2. In multiple dose studies, the pre-dosage sample must be collected immediately before the last administration of the medication.

Article 35. The collection schedule must allow an evaluable estimate of the following parameters:

I – for plasma, blood and serum: area under the curve from 0 to t (AUC_{0-t}) or 0 at the time of truncation collection ($AUC_{0-trunc}$, in the case of a truncated study), area under the curve from 0 to infinity ($AUC_{0-\infty}$), maximum concentration verified without data interpolation (C_{max}), time to reach maximum concentration (T_{max});

II – for urine: cumulative urine excretion of unaltered medicine (A_{e0-t}) and velocity of maximum urine excretion rate (Vu_{max});

III – other parameters may be requested, at Anvisa's discretion.

Article 36. The interval between periods should be at least five medicine or metabolite elimination half-lives.

Section V

Medicines that contain vitamins

Article 37. Medicines that contain vitamins associated with active pharmaceutical ingredients, which claim therapeutic properties and are not food supplements, must present BA/BE studies comparing the pharmacokinetic parameters of all active ingredients, as part of the documentation submitted for marketing authorization of synthetic medicinal products, as long as the vitamins are not biofree.

Article 38. To evaluate the comparability of vitamins, the parameters AUC_{0-t}, C_{max} and T_{max} should be used, through the quantification of the unaltered vitamin or its metabolite in the systemic circulation.

Paragraph 1. Other comparability models may be accepted, with the submission of a previous protocol for analysis by Anvisa.

Paragraph 2. To evaluate the comparability of vitamins, the articles of this Resolution that provide for endogenous substances also apply.

Section VI

Transdermal medicinal products

Article 39. The quantity of time-release drug of transdermal medicinal products must be the same between the test medicinal product and the comparator medicinal product.

Article 40. In addition to the primary parameters to determine bioequivalence (AUC_{0-t} and C_{max}), the partial AUC parameter must be considered to calculate the area from time zero to half the dosage interval (initial partial AUC) and from this to the last collection time (final partial AUC).

Article 41. The time and frequency of collections must be sufficient to adequately characterize medicine absorption, distribution, and elimination.

Article 42. The study design should be single-dose, randomized, two-treatment, two-period crossover.

Sole paragraph. Other designs may be accepted according to the characteristics of the product and upon justification.

Article 43. The study must be carried out considering the instructions regarding the location and form of application defined in the package insert of the comparator medicinal product.

Paragraph 1. The anatomic area of medication application must be the same, using the contralateral side in period 2.

Paragraph 2. The application area must have intact skin, without scars or tattoos.

Article 44. Considering that the skin condition can influence the absorption of the study medicine and, consequently, affect the efficacy and safety of the medicinal product, the degrees of skin irritation and sensitization must be evaluated.

Paragraph 1. The test medicinal product must present a lower or similar degree of skin irritation and sensitization in relation to the comparator medicinal product.

Paragraph 2. The protocols of irritability and sensitivity studies must be sent for prior analysis until the publication of a specific regulation.

Article 45. Considering the amount of medicine to be dosed into the bloodstream is dependent on the area of skin exposure to the adhesive, adhesion of the medicines to the skin should be evaluated during the conduction of the pharmacokinetic study.

Paragraph 1. Samples from all research participants must be considered in the pharmacokinetic evaluation regardless of the degree of adhesiveness of the medicinal product in use.

Paragraph 2. The protocols of the adhesion studies must be sent for prior analysis until the publication of a specific regulation.

CHAPTER V

BIOANALYTICAL STAGE OF RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE (BA/BE) STUDIES

Article 46. The bioanalytical method used to quantify the medicine in a biological matrix must be described in detail, and Collegiate Board Resolution – RDC no. 27 of 17 May 2012, or any other regulation that may succeed it, must be complied with.

Article 47. Samples from all research participants who have completed the clinical stage must be quantified.

Sole paragraph. In truncated studies, the lack of more than 10% (ten percent) of samples collected in the terminal phase of the pharmacokinetic profile should lead to the exclusion of research participant data only for the calculation of the truncated AUC parameter.

Article 48. The analysis of samples may be carried out with or without a replica.

Sole paragraph. For analysis of replicate samples, the criteria to accept the results must be previously described in the operating procedure of the site or in the study protocol.

Article 49. The lower quantification limit (LQL) defined for the method must be less than 5.00% (five percent) of the average C_{max} observed in the study for unknown samples.

Paragraph 1. If, after conducting 10.00% (ten percent) of the analytical runs, it is observed that the LQL value is greater than 5.00% (five percent) of the experimental average C_{max} obtained until that moment, a new method may be validated by considering an adequate LQL.

Paragraph 2. The results of the volunteers obtained with the first method must be considered, and the volunteers must not be reanalyzed for this reason.

Article 50. If a research participant presents interference greater than 5.00% (five percent) of his/ her C_{max} in the pre-dosage collection (time zero), considering the same period, the statistical calculation must be presented without the participant in question.

Article 51. The use of achiral bioanalytical methods is acceptable for most relative BA/BE studies; however, individual quantification of enantiomers must be performed when all the following requirements are met or unknown:

I – the enantiomers exhibit different pharmacokinetic and pharmacodynamic characteristics; and

II – the AUC ratio of the enantiomers is altered due to differences in absorption rate.

Sole paragraph. If an enantiomer is inactive or barely contributes to medicine action, it is enough to demonstrate BE for the active enantiomer only.

CHAPTER VI

STATISTICAL ANALYSIS OF RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE (BA/BE) STUDIES

Section I

Evaluation of pharmacokinetic parameters

Article 52. Pharmacokinetic parameters must be obtained from analyte concentration curves versus time and statistically analyzed to determine bioequivalence, and the following parameters must be determined:

I – area under the concentration curve versus time, calculated through trapezoid method, from time zero to time t (AUC_{0-t}), where t is the time related to the last concentration of the analyte determined experimentally (above the lower quantification limit);

II – area under the concentration curve versus time, calculated from time zero to infinite time (AUC_{0-inf}), where $AUC_{0-inf} = AUC_{0-t} + Ct/k$, where Ct is the last concentration of the analyte determined experimentally (above the quantification limit), k is the terminal phase elimination constant. The AUC_{0-t} must be equal to or greater than 80% of the AUC_{0-inf}, when truncated AUC is not used;

III – peak and time of maximum concentration (C_{max}) and (T_{max}) of the analyte, obtained directly from experimental data, without data interpolation; and

IV – elimination half-life ($t_{1/2}$) of the analyte, without the need for statistical treatment.

Sole paragraph. The area under the partial curve, from 0 (zero) to a predetermined time, must be calculated when applicable.

Article 53. For studies that use multiple doses, it must be proved that the steady state was reached after the administration of the test and comparator medicinal products, and the following parameters must be determined:

I – AUC_{0-t} calculated in the dose range (tau) at steady state;

II – C_{max} and T_{max}, obtained without data interpolation; and minimum medicinal product concentration (C_{min}), determined at the end of the steady-state dose interval;

III – average medicinal product concentration at steady state (Css = AUC_{0-t} /tau); and

IV – degree of fluctuation at steady state.

Article 54. All determinations with values lower than the lower quantification limit (LQL) should be considered equal to zero for statistical calculations.

Sole paragraph. Exceptions to the provisions in the caption of Article 54 must be justified.

Article 55. In the case of endogenous substances, the statistical analysis must be performed using plasma concentrations quantified with and without correction from baseline levels, and the conclusion of bioequivalence must be based on the corrected values.

Article 56. For studies that employ alternative designs, statistical models and appropriate parameters for their evaluation must be presented, through the prior submission of the study protocol.

Article 57. Validated statistical programs must be used for data analysis.

Article 58. The exclusion of any research participant who has completed the clinical and bioanalytical stage in accordance with the protocol prepared is not allowed.

Paragraph 1. For the exclusion of study participants, it is necessary to prove violations of criteria previously established in the study protocol.

Paragraph 2. It is not allowed to use a statistical test to identify outliers to exclude data from study participants from the statistical analysis.

Article 59. To perform the statistical analysis of BA/BE studies with pharmacokinetic outcomes:

I – a table must be presented containing individual values, (arithmetic and geometric) averages, standard deviation and coefficient of variation of all pharmacokinetic parameters related to the administration of test and comparator medicinal products;

II – AUC_{0-t} and C_{max} parameters must be transformed into natural logarithm. Justifications must be presented when a statistical analysis is chosen to be carried out in the original scale data;

III – analysis of variance (ANOVA) of the transformed primary pharmacokinetic parameters (AUC_{0-t} and C_{max}) must be performed to determine experimental error estimate. The statistical model to be used must include all possible sources of variation present in the study, as well as their interactions;

IV – a confidence interval (CI) of 90% must be built for the difference between the minimum square averages of the transformed data of the test and comparator medicinal products, for parameters AUC_{0-t} and C_{max}. The antilogarithm of the obtained CI constitutes the 90% CI for the ratio of the geometrical average of the parameters: (AUC_{0-t} test/ AUC_{0-t} comparator and C_{max} test/ C_{max} comparator). The construction of this CI must be based on the residual average square of the ANOVA obtained according to item III;

V – two formulations shall be considered bioequivalent if the extreme values of the 90% confidence interval of the geometric average ratio (AUC_{0-t} test/ AUC_{0-t} comparator and C_{max} test/ C_{max} comparator) are greater than 0.80 and lower than 1.25 (80.00-125.00%). When clinically relevant, T_{max} should be considered.

Sole paragraph. If other AUCs are used as a primary parameter, for example, partial AUC, AUC0-tau and truncated AUC, these AUCs should be considered as primary endpoint.

Section II

Determining the number of research participants

Article 60. The number of research participants must ensure sufficient statistical power to reject the null hypothesis of non-bioequivalence, and a number of less than twelve participants is not allowed.

Sole paragraph. The study protocol must establish a sufficient number of research participants in anticipation of possible dropouts and exclusions.

Article 61. To determine the number of participants in a BA/BE study, the following should be considered:

I – the estimated intra-individual coefficient of variation based on a pilot study, previous studies, or scientific literature;

II – the desired level of significance (5%);

III – the desired statistical power of at least 80%;

IV – the average deviation of the comparator product compatible with bioequivalence and with safety and efficacy; and

V – the need for the 90% confidence interval of the ratio of the geometric averages to be within the limits of bioequivalence, normally 80.00-125.00%, for transformed log data.

Paragraph 1. When reliable information on the expected variability in the parameters to be estimated is not available, a two-stage sequential study design may be used, with the prior submission of a protocol.

Paragraph 2. Individuals who present pre-dose concentrations greater than 5.00% (five percent) of C_{max} must be excluded from the statistical analysis.

Section III

High-variability medicinal products

Article 62. The extension of the confidence interval for C_{max} must be previously foreseen in the study protocol, being acceptable only for medicinal products with wide intra-individual variability and provided it is not clinically significant.

Paragraph 1. The intra-individual variability to be considered is that obtained in the study considering the intra-individual coefficient of variation (CV%) with a value greater than 30% for the comparator medicinal product.

Paragraph 2. Extending the confidence interval for C_{max} is not allowed for active pharmaceutical ingredients with a narrow therapeutic index.

Article 63. A partially replicated (three-period) or fully replicated (four-period) crossover design should be used, and the comparator medicinal product should be administered twice to each research participant.

Article 64. The extent of amplification should be defined based on the intra-individual variability of the comparator medicinal product, observed in the bioequivalence study, according to the equation [UL, LL] = exp [±k · sWR], where:

I – UL is the upper limit of the confidence interval;

II – LL is the lower limit of the confidence interval;

III - k regulatory constant of value equal to 0.760; and

IV - sWR is the intra-individual standard deviation of the comparator product for the C_{max} parameter on a logarithmic scale.

Sole paragraph. Annex I presents a table with an example model of how different CVs may lead to different acceptance limits.

Article 65. The maximum accepted magnification range is 69.84-143.19%.

Article 66. The possibility of range amplification based on high intra-individual variability does not apply to the AUC.

Article 67. The geometric average ratio of the test and comparator medicinal products must fall within the conventional acceptance range of 80.00-125.00%.

Section IV

Narrow therapeutic index (NTI) medicinal products

Article 68. In specific cases of narrow therapeutic index medicinal products, the acceptance range for AUC must be adjusted to 90.00-111.11%; the same procedure may be done with C_{max} where safety, efficacy, or monitoring level of the medicinal product is of particular importance.

CHAPTER VII

PHARMACODYNAMIC STUDIES

Section I

Design of the pharmacodynamic study

Article 69. As an alternative to pharmacokinetic studies, bioequivalence evaluation may be performed by comparing pharmacodynamic measurements.

Paragraph 1. Pharmacodynamic studies are indicated only when it is not possible to quantify the medicine in biological fluids precisely and accurately or when quantification is not sufficient to confirm the safety and efficacy of the formulation.

Paragraph 2. To conduct pharmacodynamic studies, it must be possible to obtain a dose-response curve for the purpose of comparing *in vivo* performance.

Article 70. The pharmacodynamic response must be a therapeutic or pharmacological effect related to the efficacy and/ or safety of the study medicinal product.

Sole paragraph. The pharmacodynamic response must be sensitive enough to discriminate between test and comparator medicinal product responses.

Article 71. Response should be measured quantitatively through an instrument, in a way to produce a record of pharmacodynamic measurements.

Sole paragraph. When instrumental measurements are not possible, visual scales may be used.

Article 72. Research participants must be previously evaluated, excluding those who are not considered capable of presenting the pharmacodynamic response measured.

Article 73. In determining the dose-response relationship, the doses studied should be in the steep region of the curve, in a way to avoid the administration of sub-therapeutic doses or doses that fail to differentiate pharmacodynamic responses.

Article 74. To adopt pharmacodynamic measurements, it is necessary to submit a study protocol for prior evaluation by Anvisa.

Paragraph 1. The protocols must include the proposed statistical approach and the acceptance criteria for the comparability of efficacy and safety parameters, with the due justifications.

Paragraph 2. The submission of a protocol is waived for cases already provided for in the Resolution.

Section II

Pharmacodynamic study for topical corticoids

Article 75. The pharmacodynamic study that should be used to assess the bioequivalence of topical corticoids is the vasoconstriction assay, also known as the skin brightening assay.

Sole paragraph. The assay involves applying the formulation to the skin of healthy research participants and assessing the degree of whitening of the skin after a period of product removal.

Article 76. An assessment of the degree of skin whitening must be performed instrumentally using a colorimeter or spectrophotometer that can perform readings from the CIELab system.

Article 77. Validation of methodology accuracy must be carried out in advance with six research participants, eight sites being selected (four on each forearm), and four readings performed at each site within a period of one hour.

Sole paragraph. Validation of methodology accuracy must be performed without using any formulation.

Article 78. Considering that the time to obtain a response after the application of the product may vary according to the medicine and study conditions, it is necessary to conduct a pilot study to determine the appropriate exposure time of the formulation on the skin, followed by the replicated bioequivalence study, comparing the test and comparator products.

Subsection I

Pilot study

Article 79. Different exposure times must be tested to ensure that the comparative study is performed on the linear portion of the dose-response curve.

Sole paragraph. The dose referred to in the caption of this article refers to the exposure time of the medicine on the skin.

Article 80. The study must be a single-center, randomized, open-label, prospective, one-treatment, one-period study, using the comparator medicinal product only.

Article 81. Healthy research participants who present adequate vasoconstriction with the application of corticoids should be selected.

Article 82. Six sites measuring 1.5 cm in diameter should be selected on each forearm of the research participants, which will be used to evaluate the different exposure times to be tested.

Paragraph 1. The sites must observe a distance of at least 2.5 cm from center to center and two sites must function as blank.

Paragraph 2. The sites must be located at a minimum distance of 3 to 4 cm from the research participant's wrist and elbow.

Article 83. A total of eight exposure times must be evaluated, which will be chosen in the pilot study according to the corticoid under study.

Sole paragraph. The eight different exposure times must be randomly distributed on both arms of research participants, four on each arm, with two more blanks per arm, totaling six sites per arm.

Article 84. After the exposure time adopted at each site has elapsed, the formulation must be withdrawn before measuring the pharmacodynamic response.

Article 85. The vasoconstriction reaction should be evaluated at each site 0.5 hours before applying the formulation (baseline), at the time of product withdrawal (time 0 hours) and at different times after product removal until the response return to baseline to ensure maximum pharmacodynamic response has been achieved (for example, 2, 4, 6, 19 and 24 hours).

Paragraph 1. Evaluation times are considered collection times.

Paragraph 2. The white sites must be evaluated in the same way as the other sites, considering the time before the application, the zero time and all other collection times.

Paragraph 3. The application and removal times of the formulation may be adjusted according to the medicine under study. However, at least one reading must be performed between 17 and 24 hours.

Article 86. The reading of each point, including blanks, must be done four times, using the average of the readings in data analysis.

Article 87. The method of application must be staggered, and the removal must be synchronized, and the medicine must be applied at different times (at each of the sites) and removed at the same time.

Article 88. The data obtained instrumentally from each of the eight sites must be adjusted considering the following:

I – baseline adjustment: average of the four readings performed for each collection time at each of the sites (including blank sites), subtracted from the baseline (reading 0.5 hours before applying the product); and

II – correction with blank site: the data adjusted by the baseline must be subtracted from the averages of the two blank sites (also adjusted by the baseline), considering the blanks located in the same arm and the corresponding collection times.

Article 89. The area under the effect curve ($AUEC_{0-t}$) should be calculated by using the trapezoid rule, for each application site.

Article 90. The dose-response curve must be constructed considering all points, from all individuals, simultaneously.

Article 91. The ED_{50} (time required for the degree of whitening to reach half the maximum effect predicted in a pharmacodynamic model of E_{max}) and E_{max} (Maximum bleaching effect assessed from AUEC data for each individual and site) may be obtained using a nonlinear mixed effect model considering the individual data of all participants.

Article 92. The values of ED_{50}, D1 (0.5 times ED_{50}) and D2 (2 times ED_{50}) that will be used in the comparative study must be determined.

Article 93. The following information must be presented in the statistical report:

I – tables with individual data of the readings obtained at each collection time, per exposure time;

II – tables with values corrected by the baseline and blank site;

III – table with the AUEC value obtained for each volunteer at each exposure time evaluated;

IV – table with the primary parameters E_{max} and ED_{50} summarized through descriptive statistics (Average, SD etc.); and

V – individual graphs of bleaching degree *versus* collection times for each time of exposure.

Subsection II

Comparative study

Article 94. The comparative study is of the replicated type and must be conducted with the exposure time determined by ED_{50} in the pilot study.

Article 95. The administration of medicines must be done randomly and include the following sites:

a) Test (T): Test product at exposure time corresponding to ED_{50} (two sites per arm);

b) Comparator (C): Comparator product at exposure time corresponding to ED_{50} (two sites per arm);

c) D1: comparator product at the exposure time referring to D1 (one site per arm);

d) D2: comparator product at the exposure time referring to D2 (one site per arm);

e) Blank (two sites per arm).

Article 96. The eight sites of each arm must be randomized and complementary (D1-D2, D2-D1, C-T, T-C, Blank-Blank) so that if D1 is applied to the first site of the right arm, D2 is applied to the first site of the left arm, and so on.

Article 97. The vasoconstriction reaction must be evaluated 0.5 hours before applying the formulation (basal level), at the time of product withdrawal (0 hours) and at different times after product removal, following the same application method and removal described for the pilot study.

Article 98. Data should be fitted with the baseline and blank site values, with the AUCE calculated for each site as performed in the pilot study.

Article 99. Only data from research participants considered detectors may be included in the statistical analysis.

Sole paragraph. Detector participants are those that have negative AUCE values for D1 and D2 and that meet the criterion of AUCE ratio in D2 to AUCE in D1 being greater than or equal to 1.25 (AUCE in D2/AUCE in D1 ≥ 1.25), being:

I – AUCE in D2 = 0.5 (AUCE D2 left arm + AUCE D2 right arm); and

II – AUCE in D1 = 0.5 (AUCE D1 left arm + AUCE D1 right arm).

Article 100. Only volunteers with complete data (duplicate D1 and D2 values, quadruplicate test, comparator and blank) should be included.

Article 101. The bioequivalence assessment should be performed based on the AUCE parameter in ED_{50}.

Subsection III

Statistical analysis of the comparative vasoconstriction study

Article 102. The AUCE data not transformed into ED_{50} of the test and comparator medicines should be used and calculated considering the adjustments with the value of the baseline and the blank site.

Sole paragraph. For each volunteer, the test AUCE shall be the average of the four replicates of test AUCE, and the comparator AUCE shall be the average of the four replicates of comparator AUCE.

Article 103. A 90% confidence interval should be constructed for the ratio of the test AUCE and comparator AUCE averages using the Locke method, as described in Annex II.

Article 104. The staggered average bioequivalence criterion should be adopted as the bioequivalence decision criterion.

Article 105. The following information must be presented in the statistical report:

I – tables with instrumental reading data from each collection point per exposure time (raw and adjusted data) and area under the curve; and

II – individual graphs of the bleaching degree versus the collection times for each formulation.

CHAPTER VIII

FINAL AND TRANSITIONAL PROVISIONS

Article 106. The study protocols to be submitted for prior evaluation by Anvisa must be accompanied by a submission justification and an informed consent form model.

Article 107. When any of the requirements of this Resolution are not applicable to the BA/BE study, or pharmacokinetic study, a justification for non-application of the requirement must be submitted.

Article 108. Guidelines for carrying out studies with different requirements from those established herein may be published in specific regulatory instruments, depending on the particularities of a certain medicine or medicinal product.

Article 109. All protocol deviations must be reported and justified.

Article 110. Item VI of Article 4 of the Collegiate Board Resolution – RDC 37/2011 becomes effective with the following wording:

Article 4. .....

"VI – Topical-application medicinal products, except semi-solid formulations containing corticoids, not intended for systemic effects, which contain the same medicine, at the same concentration in relation to the reference medicinal product (pharmaceutical equivalents) and excipients with the same function as those present in the comparator medicinal product." (New writing)

Article 111. Topical-application semi-solid formulations, containing corticoids already granted marketing authorization, must present the results of pharmacodynamic studies, in accordance with the provisions in this Resolution, according to the medicine present in the formulation, considering the deadlines below:

I – formulations containing betamethasone or calcipotriol – 1 July 2023;

II – formulations containing clobetasol, desonide, or fludroxycortide – 1 January 2024;

III – formulations containing dexamethasone, hydrocortisone, or mometasone – 1 July 2024; and

IV – other medicines – 1 January 2025.

Sole paragraph. Medicinal products containing combinations of different medicines must present the results of the studies considering the medicine with the first deadline imposed.

Article 112. The following are hereby revoked:

I – Collegiate Board Resolution – RDC No. 41 of 28 April 2000, published in the Federal Official Gazette No. 64 of 3 May 2000, Section 1, page 12;

II – Resolution – RE No. 898 of 29 May 2003, published in the Federal Official Gazette No. 104 of 2 June 2003, Section 1, page 54;

III – Resolution – RE No. 1,170 of 19 April 2006, published in the Federal Official Gazette No. 77 of 24 April 2006, Section 1, page 101;

IV – Article 8 of Collegiate Board Resolution – RDC No. 31 of 11 August 2010, published in the Federal Official Gazette No. 154 of 12 August 2010, Section 1, page 36.

Article 113. This Resolution enters into force on 3 July 2023.

ANTONIO BARRA TORRES

Director- President

ANNEX I

DIFFERENCES BETWEEN CVs X ACCEPTANCE LIMITS

Intra-individual CV (%)	Lower Confidence Limit	Upper Confidence Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥ 50	69.84	143.19

ANNEX II

Description of the Locke method of exact confidence interval of untransformed data for the ratio of averages of two formulations

As follows:

• n_d: number of detector volunteers in the right arm;

• n_e: number of detector volunteers in the left arm;

• X_{ijdr}: AUCE in ED_{50} of the i-th measurement of the j-th volunteer in the right arm of the comparator medicinal product, j = 1, ..., n_d and i = 1 and 2;

• X_{ijer}: AUCE in ED_{50} of the i-th measurement of the j-th volunteer in the left arm of the comparator medicinal product, j = 1, ..., n_e and i = 1 and 2;

• X_{ijdt}: AUCE in ED_{50} of the i-th measurement of the j-th volunteer in the right arm of the test formulation, j = 1, …, n_d and i = 1 and 2;

• X_{ijet}: AUCE in ED_{50} of the i-th measurement of the j-th volunteer in the left arm of the test formulation, j = 1, …, n_e and i = 1 and 2;

• µc: minimum squares average of AUCE at ED_{50} of the comparator medicinal product;

• µt: minimum squares average of AUCE in ED_{50} of the test formulation;

• q = µt/µc: minimum squares average ratio between the test formulation and the comparator medicinal product, parameter of interest.

The following measures are defined:

1) $\hat{\sigma}_{tt}^2 = \frac{1}{2n_d+2n_e-2}\left\{\sum_{j=1}^{n_d}\sum_{i=1}^{2}(X_{ijdt} - \bar{X}_{..dt})^2 + \sum_{j=1}^{n_e}\sum_{i=1}^{2}(X_{ijet} - \bar{X}_{..et})^2\right\}$:

estimated variance of the test formulation.

2) $\hat{\sigma}_{rr}^2 = \frac{1}{2n_d+2n_e-2}\left\{\sum_{j=1}^{n_d}\sum_{i=1}^{2}(X_{ijdr} - \bar{X}_{..dr})^2 + \sum_{j=1}^{n_e}\sum_{i=1}^{2}(X_{ijer} - \bar{X}_{..er})^2\right\}$:

estimated variance of the comparator medicinal product.

3) $\hat{\sigma}_{tr} = \frac{1}{2n_d+2n_e-2}\left\{\sum_{j=1}^{n_d}\sum_{i=1}^{2}(X_{ijdt} - \bar{X}_{..dt})(X_{ijdr} - \bar{X}_{..dr}) + \sum_{j=1}^{n_e}\sum_{i=1}^{2}(X_{ijet} - \bar{X}_{..et})(X_{ijer} - \bar{X}_{..er})\right\}$:

estimated covariance between the test formulation and the comparator medicinal product.

4) $\bar{X}_{..dt} = \frac{1}{2n_d}\left(\sum_{j=1}^{n_d}\sum_{i=1}^{2}X_{ijdt}\right)$:

test formulation average in the right arm.

$$5)\ \bar{X}_{..dr} = \frac{1}{2n_d}\left(\sum_{j=1}^{n_d}\sum_{i=1}^{2} X_{ijdr}\right):$$

average of the comparator medicinal product in the right arm.

$$6)\ \bar{X}_{..et} = \frac{1}{2n_e}\left(\sum_{j=1}^{n_e}\sum_{i=1}^{2} X_{ijet}\right):$$

Test formulation average in the left arm.

$$7)\ \bar{X}_{..er} = \frac{1}{2n_e}\left(\sum_{j=1}^{n_e}\sum_{i=1}^{2} X_{ijer}\right):$$

average of the comparator medicinal product in the left arm.

$$8)\ Q = \frac{\frac{1}{2n_d}+\frac{1}{2n_e}}{4}.$$

$$9)\ a = \bar{X}^2_{...r} - Qt^2_{\frac{\alpha}{2}}\hat{\sigma}^2_{rr}.$$

$$10)\ b = Qt^2_{\alpha/2}\hat{\sigma}_{tr} - \bar{X}_{...t}\bar{X}_{...r}.$$

$$11)\ c = \bar{X}^2_{...t} - Qt^2_{\frac{\alpha}{2}}\hat{\sigma}^2_{tt}.$$

$$12)\ \bar{X}_{...t} = \frac{\bar{X}_{..dt}+\bar{X}_{..et}}{2}.$$

$$13)\ \bar{X}_{...r} = \frac{\bar{X}_{..dr}+\bar{X}_{..er}}{2}.$$

14) $t_{a/2}$: 100 (1-α/2)% percentile of t distribution with $2n_d+2n_e-2$ degrees of freedom.

100 (1- α)% confidence interval for the parameter $\theta = \mu_t/\mu_r = [\theta_I; \theta_S]$, in which:

$$\theta_I = \frac{-b-(b^2-ac)^{1/2}}{a};$$

$$\theta_S = \frac{-b+(b^2-ac)^{1/2}}{a}.$$

*Locke CS. An exact confidence interval from untransformed data for the ratio of two formulation means. J Pharmacokinet Biopharm 1984; 12:649-55