COLLEGIATE BOARD RESOLUTION – RDC No. 749, DATED SEPTEMBER 5, 2022

It provides for the relative bioequivalence/bioavailability studies waiver.

The Collegiate Board of the National Health Surveillance Agency, in the use of the powers conferred on it by Art. 15, III and IV, allied to Art. 7, III and IV of Law No. 9,782, dated January 26, 1999, and to Art. 187, VI, Paragraph 1 of the Internal Regulations approved by the Collegiate Board Resolution – RDC No. 585, dated December 10, 2021, resolves to adopt the following Resolution, as discussed at a meeting held on August 31 and September 1, 2022, and I, Chief Executive Officer, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Art. 1 This Resolution provides for the criteria for the relative bioavailability/bioequivalence studies waiver.

Section II

Scope

Art. 2 This Resolution applies to generic, similar, new and innovative drugs.

Art. 3 In the case of new and innovative drugs, the relative bioavailability/bioequivalence studies waiver is applicable in the following cases:

I – biowaiver for other concentrations in relation to the concentration for which in vivo bioequivalence has been showed, in cases where the other proposed concentrations are within the approved therapeutic range, understood as the dose range for which safety and efficacy data have been presented and has been evaluated and approved by the competent federal agency, at the registration;

II – biowaiver based on the biopharmaceutical classification system and due to the dosage form, route of administration or site of action, in cases of post-registration changes, except for changes related to dosage, expansion of use, inclusion of a new route of administration, new therapeutic indication and inclusion of a new concentration for new drugs, described in the Collegiate Board Resolution – RDC No. 73, dated April 7, 2016, or another that may replace it.

Art. 4 The biowaiver of cases not described in Art. 3 of this Resolution may be accepted upon prior consultation and presentation of technical justification to the organizational unit responsible for its analysis.

CHAPTER II

GENERAL PROVISIONS

Art. 5 The company interested in the relative bioavailability/bioequivalence study waiver must submit a specific report in the registration or post-registration application, containing the technical rationale for the biowaiver based on the requirements provided for in this Resolution.

Section I

Biowaiver due to dosage form, route of administration or site of action

Art. 6 For waiver due to dosage form, route of administration or site of action, the test formulation should ideally mimic the formulation of the corresponding comparator drug.

Art. 7 Relative bioavailability/bioequivalence studies may be waived for:

I - aqueous solutions for oral use, powders or other dosage forms resulting in oral aqueous solutions before administration, which:

a) contain the same drug, in the same concentration in relation to the comparator drug (pharmaceutical equivalents); and

b) have a qualitatively identical formulation in relation to all excipients and quantitatively similar in relation to the excipients of the comparator drug that have an impact on aspects of drug absorption, such as solubility, gastrointestinal motility, transit time and intestinal permeability, including transport mechanisms;

II - parenteral use aqueous and oily solutions or other dosage forms resulting in solutions before administration, which are pharmaceutical equivalents to the comparator drug and present a qualitatively identical and quantitatively similar formulation in relation to all excipients present in the comparator drug;

III - oral inhaled drug administered via nebulizers, as well as nasal sprays and aerosols, as solutions, for local action, which are pharmaceutical equivalents to the comparator drug and present a qualitatively identical and quantitatively similar formulation in relation to all excipients present in the comparator drug;

IV - aqueous ophthalmic solutions, which are pharmaceutical equivalents to the comparator drug and present qualitatively identical and quantitatively similar formulation in relation to all excipients present in the comparator drug;

V - aqueous otological solutions that are pharmaceutical equivalents to the comparator drug and present qualitatively identical and quantitatively similar formulation in relation to all excipients present in the comparator drug;

VI - drugs for oral use that are pharmaceutical equivalents to the comparator drug and contain drugs intended for local action in the gastrointestinal tract, described in a specific normative act; or

VII - topical application dosage forms, not intended for systemic effects, which are pharmaceutical equivalents to the comparator drug and which have the same excipients in the same quantities and the same physical-chemical and microstructural behavior.

Paragraph 1 The provisions of item II do not apply to parenteral formulations containing the complexing agent cyclodextrin and its derivatives.

Paragraph 2 For the formulations referred to in Paragraph 1, the evidence for therapeutic equivalence must be previously discussed with the organizational unit responsible for analyzing the biowaiver.

Paragraph 3 The provisions of item VII do not apply to:

I - semi-solid formulations containing corticoids, otological and ophthalmic suspensions; and

II - oral inhaled aerosol drugs, oral inhalers administered via non-pressurized devices with a measured dose, suspensions administered as nasal sprays and aerosols, suspensions administered as inhalers via nebulizers and inhalation powders.

Paragraph 4 For the formulations described in item II of Paragraph 3 of this article, the therapeutic equivalence must be showed through a pharmaceutical equivalence study and pharmacokinetic or pharmacodynamic studies, as applicable, in compliance with the provisions of the Collegiate Board Resolution – RDC No. 278, dated April 16, 2019, or another that may replace it.

Art. 8 In case of waiver referred to in item I of Art. 7 of this Resolution:

I - qualitative differences in excipients with coloring, flavoring, antioxidant, acidifying, alkalizing and preservative functions may be accepted, upon presentation of technical justification; and

II - the applicant must provide rationale for the amount used of each excipient that may affect the drug's absorption, the discussion on the mechanism by which the excipient can affect the absorption and the absorption properties of the drug (rate, extent, and mechanism of absorption).

Sole paragraph. Examples of excipients affecting absorption include alcoholic sugars (e.g., mannitol and sorbitol), surfactants (e.g., polysorbate and sodium lauryl sulfate), polyethylene glycol, and ethyl alcohol.

Art. 9 In case of waiver referred to in item II of Art. 7 of this Resolution:

I - qualitative differences in excipients with acidifying, alkalizing, preservative, buffering and antioxidant functions may be accepted, provided that there is no impact on the safety and efficacy and upon presentation of a technical justification; and

II - in the case of solutions for subcutaneous or intramuscular use, the differences provided for in the previous item cannot impact the product's viscosity.

Art. 10. In case of waiver referred to in item III of Art. 7 of this Resolution:

I - quantitative differences in excipients above the criterion defined in item III of Art. 7 of this Resolution may be accepted, as long as there is no impact on the safety and efficacy and upon presentation of technical justification; and

II - regarding drug's devices in nasal sprays and aerosols, the designs of valves, pumps and actuators components must be as close as possible in all critical dimensions to those of the comparator drug.

Art. 11. In case of waiver referred to in item IV of art. 7 of this Resolution:

I - qualitative differences in excipients with a preservative, buffering, tonicity agent and thickening function may be accepted, as long as there is no impact on the safety and efficacy and upon presentation of a technical justification; and

II - the differences provided for in the previous item shall not affect the product's viscosity.

Art. 12. In case of waiver referred to in item V of Art. 7 of this Resolution, qualitative differences in excipients present in the comparator drug may be accepted, as long as there is no impact on the safety and efficacy and upon presentation of a technical justification.

Art. 13. In the event of waiver referred to in item VI of Art. 7 of this Resolution, qualitative differences in excipients present in the comparator drug may be accepted, provided that there is no impact on the safety and efficacy and upon presentation of a technical justification.

Art. 14. In the event of waiver referred to in item VII of Art. 7 of this Resolution, the biowaiver for semi-solid drugs for topical application:

I - may be accepted in the case of small differences in excipients not considered critical for skin permeation, upon prior presentation of in vitro performance data and references on the product's permeability; and

II - it will also depend on the proof of similarity between the formulations through a comparative in vitro performance test.

Art. 15. In the event of items II, III, IV, V, VI and VII of Art. 7 of this Resolution, the applicant shall provide rationale about the amount of each excipient used in the formulation.

Art. 16. Relative bioavailability/bioequivalence studies may be waived for micellar solutions intended for intravenous use whose method and administration rate are the same as the comparator drug and which meet the following criteria:

I - rapid dissociation of the micelle after dilution in plasma;

II - the main objective of the micellar system is to solubilize the drug, not being designed to control the drug's release;

III - the excipients contained in the formulation do not affect the drug's in vivo disposition;

IV - the formulation composition (micellar solution), immediately before administration, must be qualitatively identical and quantitatively similar to that of the comparator drug;

V - the pharmaceutical equivalence study proves the similarity regarding physicochemical characteristics compared to the comparator drug, including critical micelle concentration (CMC), formulation solubilization capacity, free drug, micelle size distribution, pH, osmolarity and viscosity; and

VI - the physical stability of the micellar system in all diluents must be at least equivalent to the comparator drug.

Paragraph 1 Upon technical justification, qualitative differences shall be accepted in excipients with non-critical functions in relation to the influence on the micellar system's stability and on the drug's in vivo disposition, as an acidifying, alkalizing or co-solvent agent.

Paragraph 2 In the event of Paragraph 1 of this article, the safety implications of composition differences must also be discussed.

Art. 17. For this Resolution purposes, the test drug will be considered quantitatively similar to the comparator drug when the individual amount of an excipient presents a maximum variation of ± 10% (ten percent).

Sole paragraph. If the variation referred to in the caput of this article occurs in more than one excipient, the sum of the differences must not exceed 10% (ten percent).

Art. 18. Biowaiver of other dosage forms not described in this section may be accepted upon prior consultation and presentation of a technical justification to the organizational unit responsible for the biowaiver analysis.

Section II

Biowaiver for other concentrations

Art. 19. Relative bioavailability/bioequivalence studies for other concentrations of generic, similar, innovative or new drugs may be waived for:

I - immediate release drugs, of the same dosage form and proportional formulations; and

II - modified-release drugs, of the same dosage form, same release mechanism, proportional formulations and manufactured at the same address.

Sole paragraph. The provisions of item II of the caput of this article do not apply to modified-release sterile drugs.

Art. 20. In addition to the provisions of the previous article of this Resolution, the biowaiver of the other concentrations will depend on:

I - pharmacokinetics linearity;

II - proportionality between the formulations; and

III - similarity between the different concentrations through a comparative in vitro performance test.

Sole paragraph. The provisions of this article do not apply to transdermal patches.

Art. 21. The relative bioavailability/bioequivalence study(s) may be carried out with the dosage form of higher and/or lower concentration, depending on the pharmacokinetic linearity or the safety risk of the volunteer taking part in the study.

Paragraph 1 In the case of linear pharmacokinetics, the relative bioavailability/bioequivalence study shall be carried out with the dosage form with the highest concentration, and the cases in which it is not possible to use the highest concentration in the study must be technically justified.

Paragraph 2 In the case of non-linear pharmacokinetics, the relative bioavailability/bioequivalence study shall be carried out with the dosage form with the highest concentration, when the increase in dose results in a disproportionately greater increase in the pharmacokinetic parameters for area under the curve (AUC) or maximum plasma concentration (Cmax), indicating the drug's biotransformation saturation.

Paragraph 3 The in vivo study shall be carried out with the dosage form of lower concentration when the increased dose results in a disproportionately smaller increase in the pharmacokinetic parameters for AUC or Cmax, caused by saturation of the absorption process and not by drug solubility limitation.

Paragraph 4 In the event of drug solubility limitation, the applicant must conduct relative bioavailability/bioequivalence studies with both the highest and the lowest concentration.

Art. 22. Formulations will be considered proportional when they meet at least one of the following criteria:

I - all the formulation's components are in exactly the same proportion at all different concentrations;

II - the ratio between the excipients and the total formulation weight is within the limits for moderate change of excipients established in the Collegiate Board Resolution – RDC No. 73 dated April 7, 2016, or another that may replace it; or

III - for high potency drugs (where the drug's amount in the dosage form is less than 5% (five percent) of the tablet core weight or the capsule content weight), the total weight of the dosage form must remain within around 10% (ten percent) of the total formulation weight used in the relative bioavailability/bioequivalence study and the change in concentrations can only be obtained by changing the amount of drug and diluent.

Paragraph 1 Qualitative differences are only allowed in components of immediate release drug coating, capsule shell components, coloring and flavoring agents.

Paragraph 2 In the case of drug combinations, the conditions relating to proportionality shall be met for all active substances.

Paragraph 3 In the cases provided for in Paragraph 2 of this article, when considering the amount of each active substance in a fixed combination, the other active substance(s) can be considered as excipient(s).

Paragraph 4 The exceptions to the proportionality criteria presented in this article shall be technically justified and will be evaluated, as to their relevance, by the unit responsible for biowaiver analysis.

Art. 23. For dosage forms where the dissolution study is applicable, the company shall conduct the dissolution profile study at all concentrations.

Paragraph 1 The different concentrations to undergo the dissolution study shall be analyzed according to the method approved in the product's registration and, additionally, with dissolution media pH 1.2, pH 4.5 and pH 6.8.

Paragraph 2 The applicant may justify non-profile in one of the conditions requested in Paragraph 1 of this article, considering the route of administration, the drug's absorption site, or the molecule's stability.

Paragraph 3 If the results indicate that the drug's dissolution characteristics are not pH or concentration dependent, the dissolution profiles in a medium may be sufficient for biowaiver, provided that it is duly justified.

Paragraph 4 At pH values in which the sink condition cannot be reached for all concentrations, in vitro dissolution may differ between different concentrations.

Paragraph 5 In the cases provided for in Paragraph 4 of this article, the company may show the similarity of the profiles with the same concentration using the multiple units approach (two 5 mg tablets versus one 10 mg tablet) to prove that this finding is related to the drug and not the formulation.

Paragraph 6 The similarity between the dissolution profiles for different concentrations and the concentration used as biobatch must be showed, under all the conditions tested.

Paragraph 7 The comparative dissolution profile study must comply with the provisions of the Collegiate Board Resolution – RDC No. 31, dated August 11, 2010, or any other that may replace it, and specific guidelines.

Art. 24. For dosage forms in which the dissolution study is not applicable, the similarity between the different concentrations must be proven through a comparative in vitro performance test according to a guide or specific legislation for the dosage form in question.

Art. 25. For transdermal patches with different concentrations, the pharmacokinetic study may be carried out with the highest concentration, and the others biowaived, provided that:

I - the qualitative composition of the patches is the same between the different concentrations;

II - the concentrations are proportional in relation to the effective surface area of the patch, and the lowest concentration may be considered as a partial area of the highest concentration; and

III - the formulations have similar release/dissolution profiles.

Sole paragraph. Use of a lower concentration may be justified considering the safety of research subjects.

Section III

Biowaiver based on the Biopharmaceutics Classification System (BCS)

Art. 26. The biowaiver based on the Biopharmaceutics Classification System (BCS) is a scientific approach based on the drug's aqueous solubility and intestinal permeability characteristics.

Art. 27. According to the BCS, drugs can be categorized into the following classes:

I - Class I: high solubility, high permeability;

II - Class II: low solubility, high permeability;

III - Class III: high solubility, low permeability; or

IV - Class IV: low solubility, low permeability.

Subsection I

Eligibility of medications and drugs for biowaiver by the BCS

Art. 28. The biowaiver based on the Biopharmaceutics Classification System is applicable to drugs that have high solubility with high permeability (Class I) or low permeability (Class III).

Paragraph 1 The biowaiver is applicable when the drug in the test and comparator drugs are identical.

Paragraph 2 The biowaiver is not applicable when the test drug contains an ester, ether, isomer, mixture of isomers, complex or derivative of the drug different from that contained in the comparator drug, since these differences may lead to different bioavailability not deductible through the experiments used in the biowaiver context by the BCS.

Paragraph 3 Prodrugs may be considered for biowaiver by the BCS when they are absorbed as prodrugs.

Art. 29. Biowaiver based on the biopharmaceutical classification system is applicable to immediate release drugs administered as solid oral forms or oral suspensions of systemic effect, in the same dosage form and concentration of the comparator drug and whose drug meets the solubility and permeability criteria (Classes I and III of the BCS).

Paragraph 1 The following are excluded for consideration of the biowaiver based on the BCS:

I – drugs containing medications with a low therapeutic index;

II – drugs with absorption in the oral cavity; or

III - modified release drugs.

Paragraph 2 The biowaiver based on the BCS is only applicable when the drug is administered with water.

Paragraph 3 If the drug's administration without water intake is also allowed, such as orodispersible drugs, a bioequivalence study in which the drug is administered without water intake must be conducted.

Paragraph 4 In the case of drugs formulated as fixed-dose combinations or therapeutic kits for concomitant use, the biowaiver based on the biopharmaceutical classification system will only be applicable when all the combination drugs meet the criteria defined in this Section.

Art. 30. A drug will be a candidate for biowaiver based on the biopharmaceutical classification system when, in addition to the drug(s) meeting the solubility and permeability criteria described in subsections II and III of this Section, it also meets the in vitro and excipient dissolution criteria, defined in subsections IV and V of this Section.

Subsection II

Solubility

Art. 31. A drug will be considered highly soluble if its highest dose administered orally as an immediate-release formulation (maximum dose per administration described in the package insert) is completely solubilized in up to 250 ml of each of the buffer solutions used within the physiological pH range (1.2 to 6.8), at 37 ± 1°C.

Art. 32. In cases where the highest orally administered dose does not meet the criteria described in Art. 31 of this Resolution, but the highest registered concentration of the comparator drug is soluble under the conditions described above, additional data must be submitted to justify the biowaiver approach by the BCS.

Art. 33. The proof of high solubility referred to in this Subsection must be experimentally showed by the applicant.

Art. 34. At least three pH conditions (1.2; 4.5 and 6.8) must be tested, using at least three replicates for each condition, and the coefficient of variation (CV %) must be less than 5% (five percent).

Art. 35. If the number of samples used is greater than three (n >3), all replicates must be considered in the average deviation calculation and, in addition, the solubility of the lowest solubility pH of the drug must be evaluated if contained in the specified pH range.

Sole paragraph. The experiments referred to in the caput of this article must show that the solubility is maintained for a period compatible with the expected duration of in vivo drug absorption.

Art. 36. A method for balance solubility studies, using the shake-flask technique or an alternative method, if justified, shall be used.

Art. 37. When using the shake-flask technique:

I - small volumes of solution medium can be used if the available experimental apparatus allows it;

II - the pH of each experimental solution must be recorded at the beginning, after the drug's addition, and at the balance solubility study end, to ensure that the solubility measurement was carried out at the specified pH;

III - the pH can be adjusted, if necessary; and

IV - the experiment shall be conducted for an adequate period to reach balance.

Art. 38. For active pharmaceutical ingredients known to have high solubility (BCS classes I and III), there may be a need for a large amount of active pharmaceutical ingredient (API) to observe the formation of non-dissolved solid.

Sole paragraph. In the cases provided for in the caput of this article, to avoid the large amounts of API, it is acceptable to show that the maximum dose of API per administration described in the package insert dissolves in up to 250 mL of the three buffer solutions in the established physiological pH range.

Art. 39. The lowest solubility measured in the pH range 1.2-6.8 will be used to classify the drug.

Art. 40. The solubility must be evaluated by a method appropriate to the drug's properties and buffer solutions described preferably in the Brazilian Pharmacopoeia or in other official compendia recognized by ANVISA must be used, according to Collegiate Board Resolution – RDC No. 511, dated May 27, 2021, or any other that may replace it.

Art. 41. The drug's stability under all experimental conditions must be evaluated, observing the total study duration, in at least three replicates.

Art. 42. In cases where the drug is not stable with more than 10% (ten percent) degradation of the obtained solubility value, the solubility cannot be properly determined and the drug cannot be classified.

Art. 43. The quantification method must be able to differentiate the drug from eventual degradation products.

Art. 44. For the drug's quantification, methods indicative of stability must be used and validated according to the Collegiate Board Resolution – RDC No. 166, dated July 24, 2017, or any other that may replace it.

Art. 45. In addition to experimental results, literature data can be provided to substantiate and support solubility determinations, provided they contain all the details necessary for judging the results' quality.

Subsection III

Permeability

Art. 46. Assessment of permeability should preferably be based on the extent of absorption derived from human pharmacokinetic studies, such as absolute bioavailability or mass balance.

Art. 47. It can be concluded by the high permeability, under the terms of Art. 46 of this Resolution, in the event of at least one of the following situations:

I - absolute bioavailability greater than or equal to 85% (eighty-five percent); or

II - recovery equal to or greater than 85% (eighty-five percent) of the dose administered unchanged in urine or as the sum of unchanged forms, phase I metabolites (oxidized) and phase II metabolites (conjugated) in the urine.

Paragraph 1 For metabolites in feces, only oxidized and conjugated metabolites can be considered.

Paragraph 2 Metabolites produced by reduction and hydrolysis should not be included, unless it is showed that they were not produced before absorption, such as, for example, by microbial action in the gastrointestinal tract.

Paragraph 3 Unaltered drugs in feces cannot be considered for the absorption extent determination, unless it is showed that the amount of unchanged drug to be accounted for the drug's absorption originates from biliary excretion, intestinal secretion or unstable metabolites, as is the case of metabolites that were converted back into the parent compound by the action of microorganisms.

Art. 48. Data from in vivo pharmacokinetic studies in humans obtained from indexed scientific literature can be accepted, provided they contain all the details necessary for judging the results' quality.

Art. 49. Permeability can also be evaluated by standardized and validated in vitro methods using Caco-2 cells, as described in Normative Instruction - NI No. 182, dated September 5, 2022, or any other that may replace it.

Paragraph 1 The results of permeability assays with Caco-2 cells must be discussed in the context of available pharmacokinetic data in humans.

Paragraph 2 If high permeability is inferred by the in vitro assay with a cell system, it must be showed that the permeability is independent of active transport.

Art. 50. If high permeability is not showed, the drug is considered to be of low permeability for classification purposes by the BCS.

Art. 51. Additional drug's stability data in the gastrointestinal tract may be necessary and the following conditions must be observed:

I - if mass balance is used to show high permeability, the drug's stability in the gastrointestinal tract must be demonstrated, unless a dose equal to or greater than 85% (eighty-five percent) is recovered unchanged in the urine;

II - when the demonstration of high permeability is supported by Caco-2 cell assays, the stability evaluation in the gastrointestinal tract is required;

III - stability in the gastrointestinal tract can be documented using compendial or simulated intestinal and gastric fluids, but other relevant methods can be used when duly justified;

IV - the solution containing the drug must be incubated at 37°C for a period representing the drug's contact with the respective body fluids, such as one hour in the gastric fluid and three hours in the intestinal fluid;

V - the drug's concentration must be determined by a validated method; and

VI - a significant drug degradation, above 10% (ten percent), prevents the high permeability classification by the BCS.

Subsection IV

In vitro dissolution

Art. 52. The comparative dissolution profile study for biowaiver based on the BCS shall be conducted with a batch representative of the proposed manufacturing process for the test drug compared to the comparator drug.

Sole paragraph. The test drug must originate from a batch of at least 1/10 (one tenth) of the production scale or 100,000 (one hundred thousand) units, whichever is greater, unless justified.

Art. 53. Dissolution profile studies must meet the requirements of the Collegiate Board Resolution – RDC No. 31, dated August 11, 2010, or any other that may replace it, with the exception of dissolution methods that must follow the conditions provided for in this Resolution.

Sole paragraph. The comparative dissolution profile study must be carried out with the same batches of test and comparator drugs used for the pharmaceutical equivalence evaluation.

Art. 54. In the dissolution profile study, the following experimental conditions must be met:

I - apparatus and stirring speed: shovel at 50 rpm or basket at 100 rpm;

II - dissolution means: pH 1.2, pH 4.5 and pH 6.8, additional investigation may be required in the pH of lower solubility, if different from those described;

III - temperature: 37 ± 1ºC;

IV - the preparation and dissolution means must preferably follow what is described in the Brazilian Pharmacopoeia or, in its absence, in other official compendia recognized by ANVISA, according to Collegiate Board Resolution – RDC No. 511, dated May 27, 2021, or any other that may replace it;

V - pH record at the beginning and end of the experiment; and

VI - medium volume of 900 mL or less, and it is recommended to use the volume selected for the quality control test.

Paragraph 1 Use of surfactants and organic solvents in the dissolution medium is prohibited.

Paragraph 2 Use of enzymes may be accepted only in the case of gelatin capsules and gelatin-coating tablets when cross-linking is showed, if properly justified.

Paragraph 3 The samples must be filtered during collection, except when in situ detection methods are used.

Paragraph 4 When high variability or cone formation (coning) is noted with a shovel apparatus at 50 rpm, both for the comparator drug and for the test drug, a basket apparatus at 100 rpm is recommended.

Paragraph 5 In addition to the provisions of Paragraph 4 of this article, alternative methods, such as the use of anchors (sinkers) or another appropriate approach, may be considered to overcome problems such as cone formation and may be accepted, upon presentation of a technical justification that will be assessed by the organizational unit responsible for the biowaiver analysis.

Art. 55. The methods used to quantify the drug must be appropriate and validated according to Collegiate Board Resolution – RDC No. 166, dated July 24, 2017, or any other that may replace it.

Art. 56. For drugs containing Class I drugs, the test and comparator drugs must either present a very fast dissolution (minimum 85% dissolution within 15 minutes) or rapid dissolution (minimum 85% dissolution within 30 minutes).

Sole paragraph. Similarity must be showed between the dissolution profiles of the test and comparator drugs under all conditions tested.

Art. 57. In cases where one drug has fast dissolution and the other a very fast dissolution for Class I drugs, the similarity of the profiles must be demonstrated according to the guidelines defined in the Collegiate Board Resolution – RDC No. 31, dated August 11, 2010, or any other that may replace it.

Art. 58. For drugs containing Class III drugs, the test and comparator drugs must both show a very fast dissolution (minimum 85% dissolution within 15 minutes) under the conditions defined in this subsection.

Art. 59. For drugs containing fixed-dose combinations (FDCs), dissolution profiles must meet the approval criteria for all drugs present in the combination.

Paragraph 1 Drugs with FDC containing only Class I drugs must meet the dissolution criteria for Class I drugs of the BCS.

Paragraph 2 Drugs with FDC containing only Class III drugs must meet the dissolution criteria defined for Class III drugs of the BCS.

Paragraph 3 For drugs with FDC containing Class I and Class III drugs, the dissolution criteria corresponding to the BCS Class of each combination drug must be applied.

Art. 60. For drugs with more than one concentration, the biowaiver approach based on the BCS must be applied for each concentration, that is, similarity of the dissolution profiles of the test and comparator drug must be demonstrated for each concentration, according to the criteria defined in this Section.

Subsection V

Excipients

Art. 61. The test formulation should ideally mimic the comparator drug formulation.

Art. 62. The applicant shall provide information about the function of each excipient, as well as justification of the amount used.

Art. 63. In cases where there is a difference between excipients, their potential to affect in vivo absorption must be evaluated, considering the drug's properties and the excipients effects.

Sole paragraph. It must be justified why the proposed differences do not affect the absorption profile of the drug in question, using mechanistic approaches and based on risk assessment, taking into account:

I - the amount of excipient used;

II - the mechanism by which the excipient can affect absorption; and

III - the drug's absorption properties (rate, extent, and absorption mechanism).

Art. 64. The possible effects of excipients on aspects of in vivo absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability, including transport mechanisms, should be considered.

Sole paragraph. Excipients affecting aspects of in vivo absorption include, but are not limited to, alcoholic sugars such as mannitol and sorbitol, and surfactants such as sodium lauryl sulfate.

Art. 65. In the case of immediate release oral drugs containing the drug isoniazid, an eventual drug-excipient interaction, with the consequent impact on bioavailability, must be avoided, and saccharides, such as lactose and sucrose, must not be used as excipients.

Art. 66. For Class I drugs, qualitative and quantitative differences are allowed, except for excipients that may affect the rate or extent of drug absorption, which must be qualitatively the same and quantitatively similar, with a difference of at most 10% in relation to the comparator drug.

Sole paragraph. In addition to the provisions of the caput of this article, the cumulative difference for excipients affecting absorption must be up to 10% (ten percent).

Art. 67. For Class III drugs, all excipients must be qualitatively the same and quantitatively similar to the comparator drug.

Paragraph 1 The caput provisions do not apply to the components of the capsule shell and coating.

Paragraph 2 Differences in dye, flavoring and preservatives may be allowed when they represent a very small amount in the formulation.

Paragraph 3 Excipients that can affect absorption must be qualitatively the same and quantitatively similar, with a difference of at most 10% (ten percent) in relation to the comparator drug and, additionally, the cumulative difference for these excipients must be up to 10% (ten percent).

Paragraph 4 In addition to the Paragraph 3 provisions of this article, the quantitative differences of the other excipients may not exceed the criteria provided for in the Attachment to this Resolution.

Art. 68. Biowaiver based on the BCS is applicable to drugs containing FDC of the same dosage form and concentration.

Paragraph 1 For drugs with FDC containing only Class I drugs, the criteria for excipients defined for Class I drugs must be met.

Paragraph 2 For drugs with FDC containing only Class III drugs or Class I and Class III drugs, the criteria for excipients defined for Class III drugs must be met.

CHAPTER III

TRANSITIONAL AND FINAL PROVISIONS

Art. 69. Biowaiver will be accepted under the terms of the Collegiate Board Resolution – RDC No. 37, dated August 3, 2011, for registration petitions and post-registration changes filed up to 12 (twelve) months from the validity of this Resolution, in the following cases:

I - drugs containing medications listed in Normative Instruction No. 10, dated September 29, 2016;

II - dosage forms that are candidates for biowaiver listed in Chapter II, Section I, of this Resolution; and

III - biowaiver of the different concentrations, as provided for in Chapter II, Section II, of this Resolution.

Art. 70. Compliance with the technical criteria established in this Resolution may be waived provided that they are addressed by alternative approaches or if they are considered inapplicable to the product subject to regularization, upon technical justification.

Art. 71. The specific biowaiver report will be rejected when the criteria established in this Resolution are not met or the technical justification is rejected under the terms of Art. 70 of this Resolution.

Art. 72. ANVISA may, at any time and at its discretion, require additional evidence of identity and quality of the components of an approved drug through the biowaiver mechanism, or require new evidence for safety and efficacy proof, including the bioequivalence study itself, in the event of new facts that give rise to further assessments, even after the registration is granted.

Art. 73. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, under the terms of Law No. 6,437, dated August 20, 1977, without prejudice to applicable civil and criminal liabilities.

Art. 74. The following are hereby revoked:

I - Collegiate Board Resolution – RDC No. 37, dated August 3, 2011, published in the Federal Official Gazette No. 150, dated August 5, 2011, Section 1, page 117;

II - Normative Instruction - NI No. 10, dated September 29, 2016, published in the Federal Official Gazette No. 189, dated September 30, 2016, Section 1, page 98;

III - item I of Article 26 of the Collegiate Board Resolution – RDC No. 31, dated August 11, 2010, published in the Federal Official Gazette No. 154, dated August 12, 2010, Section 1, page 36; and

IV - Article 12 of the Collegiate Board Resolution – RDC No. 278, dated April 16, 2019, published in the Federal Official Gazette No. 74, dated April 17, 2019, Section 1, page 200.

Art. 75. This Resolution shall enter into force on October 3, 2022.

ANTONIO BARRA TORRES

Director-President

ATTACHMENT

Criteria to demonstrate quantitative similarity for drugs containing Class III drugs.

Within the quantitative similarity context, differences in excipients for drugs containing Class III drugs should not exceed the following targets:	
Class of excipients	**% of the excipient in the comparator drug**
1. Excipients that may affect absorption	
1.1 By excipient	10%
1.2 Sum of differences:	10%
	Percentage difference in relation to core weight* (w/w)
2. All excipients:	
2.1 Diluent	10%
2.2 Disintegrating agent	
2.2.1 Starch	6%
2.2.2 Others	2%
2.3 Binder	1%
2.4 Lubricant	
2.4.1 Stearates	0.5%
2.4.2 Others	2%
2.5 Sliders	
2.5.1 Talc	2%
2.5.2 Others	0.2%
3. % total change allowed for all excipients (including excipients that may affect absorption):	10%

*Note: Core does not include tablet coating film or capsule shell.