COLLEGIATE BOARD RESOLUTION – RDC No. 749 OF 5 SEPTEMBER 2022

Provides for waiver from bioequivalence/relative bioavailability studies.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 7, items III and IV, and Article 15, items III and IV of Law no. 9,782 of 26 January 1999, and Article 187, item VI, Paragraph 1 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 31 August and 1 September 2022, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 1. This Resolution establishes the criteria for waiver from relative bioavailability/bioequivalence studies.

Section II

Scope

Article 2. This Resolution applies to generic, similar, new, and innovative medicinal products.

Article 3. In the case of new and innovative medicinal products, the waiver from relative bioavailability/bioequivalence studies is applicable in the following cases:

I – biowaiver for other concentrations in relation to the concentration for which *in vivo* bioequivalence was demonstrated, 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 these have been evaluated and approved by the competent federal agency at the time of marketing authorization;

II – biowaiver based on the biopharmaceutical classification system and based on the dosage form, route of administration, or site of action, in cases of post-marketing authorization changes, except changes related to dosage, expanded use, inclusion of a new route of administration, new therapeutic indication, and inclusion of a new concentration for new medicinal products, as described in Collegiate Board Resolution – RDC No. 73 of 7 April 2016, or any other resolution that may replace it.

Article 4. Biowaiver for cases not described in Article 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

Article 5. Companies interested in obtaining waiver from the relative bioavailability/bioequivalence study must submit a specific report in the application for marketing authorization or post-marketing authorization, containing the technical rationale for the biowaiver based on the requirements provided for in this Resolution.

Section I

Biowaiver based on dosage form, route of administration, or site of action

Article 6. For waiver based on dosage form, route of administration, or site of action, the test formulation should ideally mimic the formulation of the corresponding comparator medicinal product.

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

I – oral aqueous solutions, powders, or other dosage forms that result in oral aqueous solutions prior to administration, which:

a) contain the same drug, in the same concentration as the comparator medicinal product (pharmaceutical equivalents); and

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

II – aqueous and oily solutions for parenteral use or other pharmaceutical forms that result in solutions before administration, which are pharmaceutical equivalents to the comparator medicinal product and have a qualitatively identical and quantitatively similar formulation regarding all excipients present in the comparator medicinal product;

III – oral inhaled medications administered via nebulizers, as well as nasal sprays and aerosols, in the form of solutions, for local action, which are pharmaceutical equivalents to the comparator medicinal product and have a qualitatively identical and quantitatively similar formulation regarding all excipients present in the comparator medicinal product;

IV – aqueous ophthalmic solutions, which are pharmaceutical equivalents to the comparator medicinal product and have a qualitatively identical and quantitatively similar formulation regarding all excipients present in the comparator medicinal product;

V – aqueous otological solutions that are pharmaceutical equivalents to the comparator medicinal product and have a qualitatively identical and quantitatively similar formulation regarding all excipients present in the comparator medicinal product;

VI – oral medications that are pharmaceutical equivalents to the comparator medicinal product and contain drugs intended for local action in the gastrointestinal tract, as described in a specific regulatory act; or

VII – topical dosage forms, not intended for systemic effects, that are pharmaceutical equivalents to the comparator medicinal product and that contain 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, evidence for therapeutic equivalence must be discussed in advance 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 corticosteroids, otological and ophthalmic suspensions; and

II – oral inhaled aerosol medications, oral inhalers administered via non-pressurized metered-dose devices, 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, therapeutic equivalence must be demonstrated through a pharmaceutical equivalence study and pharmacokinetic or pharmacodynamic studies, as applicable, in accordance with the provisions of Collegiate Board Resolution – RDC No. 278 of 16 April 2019, or any other resolution that may replace it.

Article 8. In the event of a waiver referred to in Item I of Article 7 of this Resolution:

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

II – the applicant must present justification for the quantity used of each excipient that may affect drug absorption, a discussion of the mechanism through which the excipient may affect absorption, and the drug's absorption properties (rate, extent, and mechanism of absorption).

Sole paragraph. Examples of excipients that affect absorption include sugar alcohols (for example, mannitol and sorbitol), surfactants (for example, polysorbate and sodium lauryl sulfate), polyethylene glycol, and ethyl alcohol.

Article 9. In the event of a waiver referred to in Item II of Article 7 of this Resolution:

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

II – in the case of solutions for subcutaneous or intramuscular use, the differences provided for in the previous item may not impact the viscosity of the product.

Article 10. In the event of a waiver referred to in Item III of Article 7 of this Resolution:

I – quantitative differences in excipients above the criterion defined in Item III of Article 7 of this Resolution may be accepted, provided there is no impact on safety and efficacy and upon presentation of technical justification; and

II – regarding the devices of nasal sprays and aerosols, the designs of the components (valve, pump, and actuator) must be as close as possible in all critical dimensions to those of the comparator medicinal product.

Article 11. In the event of a waiver referred to in Item IV of Article 7 of this Resolution:

I – qualitative differences in excipients with preservative, buffering, tonicity, and thickening functions may be accepted, provided there is no impact on safety and efficacy and upon presentation of technical justification; and

II – the differences provided for in the previous item may not impact the viscosity of the product.

Article 12. In the event of a waiver referred to in Item V of Article 7 of this Resolution, qualitative differences in excipients present in the comparator medicinal product may be accepted, provided there is no impact on safety and efficacy and upon presentation of technical justification.

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

Article 14. In the event of a waiver referred to in Item VII of Article 7 of this Resolution, the biowaiver for semi-solid medicinal products 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 product permeability; and

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

Article 15. In the event of items II, III, IV, V, VI, and VII of Article 7 of this Resolution, the applicant must present a justification for the quantity of each excipient used in the formulation.

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

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

II – the main purpose of the micellar system is to solubilize the drug and is not designed to control drug release;

III – the excipients contained in the formulation do not affect the *in vivo* disposition of the medicine;

IV – the composition of the formulation (micellar solution), immediately prior to administration, must be qualitatively identical and quantitatively similar to that of the comparator medicinal product;

V – the pharmaceutical equivalence study verifies the similarity in physicochemical characteristics compared to the comparator medicinal product, including the critical micelle concentration (CMC), solubilization capacity of the formulation, free and bound 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 that of the comparator medicinal product.

Paragraph 1. Upon technical justification, qualitative differences in excipients with non-critical functions regarding the influence on the stability of the micellar system and the *in vivo* disposition of the medicinal product, such as acidifying, alkalizing, or co-solvent agents, may be accepted.

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

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

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

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

Section II

Biowaiver for other concentrations

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

I – immediate-release medicinal products with the same dosage form and proportional formulations; and

II – modified-release medicinal products with the same dosage form, the same release mechanism, proportional formulations, and produced at the same address.

Sole Paragraph. The provisions of Item II of the caption of this article do not apply to sterile modified-release medicinal products.

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

I – linearity of pharmacokinetics;

II – proportionality between formulations; and

III – similarity between different concentrations through comparative *in vitro* performance testing.

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

Article 21. The relative bioavailability/bioequivalence study(ies) may be conducted with the pharmaceutical form of the highest and/or lowest concentration, depending on the pharmacokinetic linearity or the risk to the safety of the volunteer participating in the study.

Paragraph 1. In the case of linear pharmacokinetics, the relative bioavailability/bioequivalence study must be conducted with the pharmaceutical form of the highest concentration, and 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 nonlinear pharmacokinetics, the relative bioavailability/bioequivalence study must be performed with the highest concentration dosage form when increasing the dose results in a disproportionately greater increase in the pharmacokinetic parameters area under the curve (AUC) or maximum plasma concentration (C_{max}), indicating saturation of the medicinal product's biotransformation.

Paragraph 3. The *in vivo* study must be performed with the lowest concentration dosage form when increasing the dose results in a disproportionately smaller increase in the pharmacokinetic parameters AUC or C_{max}, caused by saturation of the absorption process and not by limitation of the medicinal product's solubility.

Paragraph 4. In the event of limited medicinal product solubility, the applicant must conduct relative bioavailability/bioequivalence studies with both the highest and lowest concentrations.

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

I – all components of the formulation are in exactly the same proportion across all different concentrations;

II – the ratio of excipients to the total weight of the formulation is within the limits for moderate excipient changes established in Collegiate Board Resolution – RDC No. 73 of 7 April 2016, or any other resolution that may replace it; or

III – for high-potency medicines (in which the amount of drug in the dosage form is less than 5% (five percent) of the tablet core weight or the weight of the capsule contents), the total weight of the dosage form must remain within plus or minus 10% (ten percent) of the total weight of the formulation used in the relative bioavailability/bioequivalence study, and the alteration between concentrations can only be obtained by changing the amount of drug and diluent.

Paragraph 1. Qualitative differences are permitted only in components of the coating of immediate-release medicinal products, components of the capsule shell, colorants, and flavorings.

Paragraph 2. In the case of medicinal product combinations, the conditions related to proportionality must be met for all active substances.

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

Paragraph 4. Exceptions to the proportionality criteria presented in this article must be technically justified and will be evaluated for relevance by the unit responsible for analyzing the biowaiver.

Article 23. For dosage forms to which the dissolution study is applicable, the company must conduct the dissolution profile study in all concentrations.

Paragraph 1. The different concentrations to be subjected to the dissolution study must be analyzed according to the method approved in the product marketing authorization and, additionally, with dissolution media at pH 1.2, pH 4.5, and pH 6.8.

Paragraph 2. The applicant may justify not performing a profile under one of the conditions requested in Paragraph 1 of this article by considering the route of administration, the site of drug absorption, or molecule stability.

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

Paragraph 4. At pH values where the sink condition cannot be achieved 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 demonstrate the similarity of the profiles with the same concentration using the multiple-unit 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 between the different concentrations and the concentration used as a biobatch must be demonstrated, under all conditions tested.

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

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

Article 25. For transdermal patches with different concentrations, the pharmacokinetic study may be performed with the highest concentration, with the remaining concentrations being bio-waived, provided that:

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

II – the concentrations are proportional to the effective surface area of the patch, with the lowest concentration being considered a partial area of the highest concentration; and

III – the formulations present similar release/dissolution profiles.

Sole paragraph. The use of a lower concentration may be justified by considering the safety of research participants.

Section III

Biowaiver based on the Biopharmaceutical Classification System (BPS)

Article 26. Biowaiver based on the Biopharmaceutical Classification System (BPS) is a scientific approach based on the drug's aqueous solubility and intestinal permeability characteristics.

Article 27. According to the BPS, 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 drugs and medicinal products for biowaiver by the BPS

Article 28. Biowaiver based on the biopharmaceutical classification system applies to drugs that present high solubility with high permeability (Class I) or low permeability (Class III).

Paragraph 1. Biowaiver is applicable when the drug in the test and comparator medicinal products are identical.

Paragraph 2. Biowaiver is not applicable when the test medicinal product contains an ester, ether, isomer, mixture of isomers, complex, or derivative of the drug different from that contained in the comparator medicinal product, since these differences may lead to different bioavailability values that cannot be deduced through the experiments used in the context of biowaiver by the BPS.

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

Article 29. Bioexemption based on the biopharmaceutical classification system is applicable to immediate-release medicinal products administered as solid oral forms or oral suspensions with systemic effect, in the same pharmaceutical form and concentration as the comparator medicinal product and whose drug meets the solubility and permeability criteria (Classes I and III of the BPS).

Paragraph 1. The following are excluded from consideration for biowaiver based on the BPS:

I – medicinal products containing drugs with a low therapeutic index;

II – medicinal products absorbed in the oral cavity; or

III – modified-release medicinal products.

Paragraph 2. Biowaiver based on the BPS is only applicable when the medicinal product is administered with water.

Paragraph 3. If administration of medicinal products without water is also permitted, such as orodispersible medicinal products, a bioequivalence study in which the medication is administered without water must be conducted.

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

Article 30. A medicinal product will be a candidate for biowaiver based on the biopharmaceutical classification system when, in addition to 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

Article 31. A drug will be considered highly soluble if its largest 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.

Article 32. In cases where the largest dose administered orally does not meet the criteria described in Article 31 of this Resolution, but the highest recorded concentration of the comparator medicinal product is soluble under the conditions described above, additional data must be submitted to justify the BPS's biowaiver approach.

Article 33. The applicant must demonstrate experimentally the high solubility referred to in this Subsection.

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

Article 35. If more than three samples are used (n>3), all replicates must be considered in calculating the mean deviation. Additionally, the solubility at the pH of the drug's lowest solubility must be evaluated if it is within the specified pH range.

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

Article 36. A method for equilibrium solubility studies must be used, using the shake-flask technique or an alternative method, if justified.

Article 37. When using the shake-flask technique:

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

II – the pH of each experimental solution must be recorded at the beginning, after the addition of the drug, and at the end of the equilibrium solubility study, to ensure that the solubility measurement was conducted at the specified pH;

III – the pH may be adjusted, if necessary; and

IV – the experiment must be conducted for an adequate period to achieve equilibrium.

Article 38. For active pharmaceutical ingredients known to have high solubility (classes I and III of the BPS), a large amount of active pharmaceutical ingredient (API) may be required to observe the formation of undissolved solids.

Sole paragraph. In the cases provided for in the caption of this article, to avoid the use of large amounts of the API, it is acceptable to demonstrate that the maximum dose of the 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.

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

Article 40. Solubility must be assessed using a method appropriate to the drug's properties, and buffer solutions described preferably in the Brazilian Pharmacopoeia or other official compendia recognized by Anvisa must be used, in accordance with Collegiate Board Resolution – RDC No. 511 of 27 May 2021, or any other resolution that may replace it.

Article 41. Drug stability must be assessed under all experimental conditions, observing the total duration of the study, in at least three replicates.

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

Article 43. The quantification method must be capable of differentiating the drug from potential degradation products.

Article 44. For drug quantification, methods indicative of stability and validated in accordance with Collegiate Board Resolution – RDC No. 166 of 24 July 2017 or any other resolution that may replace it, must be used.

Article 45. In addition to experimental results, literature data may be provided to substantiate and support solubility determinations, provided they contain all the details necessary to assess the quality of the results.

Subsection III

Permeability

Article 46. The permeability assessment should preferably be based on the extent of absorption derived from pharmacokinetic studies in humans, such as absolute bioavailability or mass balance.

Article 47. High permeability may be concluded, in accordance with Article 46 of this Resolution, when at least one of the following situations occurs:

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 administered dose in unchanged form in urine or as the sum of the unchanged forms, phase I metabolites (oxidized), and phase II metabolites (conjugates) in urine.

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

Paragraph 2. Metabolites produced by reduction and hydrolysis should not be included unless demonstrated that they were not produced prior to absorption, such as by microbial action in the gastrointestinal tract.

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

Article 48. Data from *in vivo* pharmacokinetic studies in humans obtained from indexed scientific literature may be accepted, provided they contain all the details necessary to assess the quality of the results.

Article 49. Permeability may also be assessed by standardized and validated *in vitro* methods using Caco-2 cells, as described in Normative Instruction – IN No. 182 of 5 September 2022, or any other that may replace it.

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

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

Article 50. If high permeability is not demonstrated, the drug is considered to have low permeability for BPS classification purposes.

Article 51. Additional data on drug stability in the gastrointestinal tract may be necessary, and the following conditions must be met:

I – if mass balance is used to demonstrate 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 tests with Caco-2 cells, an assessment of stability 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 may be used when duly justified;

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

V – the drug concentration must be determined using a validated method; and

VI – significant drug degradation, above 10% (ten percent), precludes classification of high permeability by the BPS.

Subsection IV

***In vitro* dissolution**

Article 52. The comparative dissolution profile study for biowaiver purposes based on the BPS must be conducted with a representative batch of the proposed manufacturing process for the test medicinal product compared to the comparator medicinal product.

Sole paragraph. The test medicinal product 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.

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

Sole paragraph. The comparative dissolution profile study must be performed with the same batches of test and comparator medicinal products used to assess pharmaceutical equivalence.

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

I – apparatus and agitation speed: paddle at 50 rpm or basket at 100 rpm;

II – dissolution media: pH 1.2, pH 4.5, and pH 6.8. Additional investigation may be required at the pH of lowest solubility if different from those described herein;

III – temperature: 37 ± 1°C;

IV – preparation and dissolution media should preferably follow those described in the Brazilian Pharmacopoeia or, in its absence, in other official compendia recognized by Anvisa, in accordance with Collegiate Board Resolution – RDC No. 511 of 27 May 2021, or any other resolution that may replace it;

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

VI – volume of the medium of 900 mL or less, with the volume selected for the quality control test being recommended.

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

Paragraph 2. The use of enzymes may only be accepted for gelatin capsules and gelatin-coated tablets when cross-linking is demonstrated, if appropriately justified.

Paragraph 3. Samples must be filtered during collection, except when *in situ* detection methods are employed.

Paragraph 4. When high variability or coning is observed using a paddle apparatus at 50 rpm, for both the comparator and the test medicinal product, the use of 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 sinkers or another appropriate approach, may be considered to overcome problems such as coning and may be accepted, upon presentation of technical justification that will be evaluated by the organizational unit responsible for analyzing the biowaiver.

Article 55. The methods used to quantify the medicine must be appropriate and validated in accordance with Collegiate Board Resolution – RDC No. 166 of 24 July 2017, or any other resolution that may replace it.

Article 56. For medications containing Class I drugs, the test and comparator medicinal products must both exhibit very rapid dissolution (minimum 85% dissolution within 15 minutes) or rapid dissolution (minimum 85% dissolution within 30 minutes).

Sole paragraph. Similarity between the dissolution profiles of the test and comparator medicinal products must be demonstrated under all tested conditions.

Article 57. In cases where one medicine exhibits rapid dissolution and the other very rapid dissolution for Class I drugs, the similarity of the profiles must be demonstrated in accordance with the guidelines defined in Collegiate Board Resolution – RDC No. 31 of 11 August 2010, or any other resolution that may replace it.

Article 58. For medications containing Class III drugs, the test and comparator medicinal products must both exhibit very rapid dissolution (minimum 85% dissolution within 15 minutes) under the conditions defined in this subsection.

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

Paragraph 1. Medications with FDCs containing only Class I drugs must meet the dissolution criteria for Class I drugs of the BPS.

Paragraph 2. Medications with FDCs containing only Class III drugs must meet the dissolution criteria defined for Class III drugs of the BPS.

Paragraph 3. For medications with FDCs containing both Class I and Class III drugs, the dissolution criteria corresponding to the BPS Class of each drug in the combination must be applied.

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

Subsection V

Excipients

Article 61. The test formulation should ideally mimic the formulation of the comparator medicinal product.

Article 62. The applicant must present information about the function of each excipient, as well as justification for the quantity used.

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

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

I – the quantity of excipient used;

II – the mechanism by which the excipient may affect absorption; and

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

Article 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 that affect aspects of *in vivo* absorption include, but are not limited to, sugar alcohols, such as mannitol and sorbitol, and surfactants, such as sodium lauryl sulfate.

Article 65. In the case of immediate-release oral medications containing isoniazid, potential drug-excipient interactions, with their consequent impact on bioavailability, must be avoided. Saccharides, such as lactose and sucrose, must not be used as excipients.

Article 66. For Class I drugs, qualitative and quantitative differences are permitted, 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 no more than 10% compared to the comparator medicinal product.

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

Article 67. For Class III drugs, all excipients must be qualitatively the same and quantitatively similar to the comparator medicinal product.

Paragraph 1. The provisions in the caption of this article do not apply to the components of capsule shell and coating.

Paragraph 2. Differences in colorants, flavorings, and preservatives may be permitted when they represent a very small amount in the formulation.

Paragraph 3. Excipients that may affect absorption must be qualitatively the same and quantitatively similar, with a difference of no more than 10% (ten percent) compared to the comparator medicinal product. Additionally, the cumulative difference for these excipients must be up to 10% (ten percent).

Paragraph 4. In addition to the provisions in Paragraph 3 of this article, the quantitative differences of the other excipients may not exceed the criteria set forth in the Annex to this Resolution.

Article 68. The biowaiver based on the BPS applies to medicinal products containing FDC of the same pharmaceutical form and concentration.

Paragraph 1. For FDC medicinal products containing only Class I drugs, the excipient criteria defined for Class I drugs must be met.

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

CHAPTER III

TRANSITIONAL AND FINAL PROVISIONS

Article 69. Biowaiver will be accepted in accordance with Collegiate Board Resolution – RDC No. 37 of 3 August 2011, for marketing authorization requests and post-marketing authorization

changes filed up to 12 (twelve) months from the effective date of this Resolution, in the following cases:

I – medicinal products containing drugs listed in Normative Instruction No. 10 of 29 September 2016;

II – pharmaceutical forms eligible for biowaiver listed in Chapter II, Section I, of this Resolution; and

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

Article 70. Compliance with the technical criteria provided for in this Resolution may be waived if they are overcome by alternative approaches or if they are deemed inapplicable to the product subject to regularization, with a substantiated technical justification.

Article 71. The specific biowaiver report will be rejected if the criteria provided for in this Resolution are not met or if the technical justification is rejected in accordance with Article 70 of this Resolution.

Article 72. Anvisa may, at any time and at its discretion, require additional proof of identity and quality of the components of a medicinal product approved through the biowaiver mechanism, or request new evidence to demonstrate safety and efficacy, including the bioequivalence study itself, if new facts arise that give rise to additional evaluations, even after the marketing authorization has been granted.

Article 73. Failure to comply with the provisions contained in this Resolution constitutes a health violation, in accordance with Law No. 6,437 of 20 August 1977, without prejudice to applicable civil and criminal liabilities.

Article 74. The following are hereby revoked:

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

II – Normative Instruction – IN No. 10 of 29 September 2016, published in the Federal Official Gazette No. 189 of 30 September 2016, Section 1, page 98;

III – Item I of Article 26 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; and

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

Article 75. This Resolution shall come into effect on 3 October 2022.

ANTONIO BARRA TORRES

Director-President

ANNEX

Criteria for demonstrating quantitative similarity for medicinal products containing Class III drugs.

Within the context of quantitative similarity, differences in excipients for medicinal products containing Class III drugs should not exceed the following targets:	
Excipient class	% of the amount of excipient in the comparator medicinal product
1. Excipients that may affect absorption	
1.1 Per excipient	10%
1.2 Sum of differences:	10%
	Percentage difference in relation to the core weight* (w/w)
2. All excipients:	
2.1 Diluent	10%
2.2 Disintegrant	
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 Glidants	
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: The core does not include tablet coating film or capsule shell.