COLLEGIATE BOARD RESOLUTION - RDC NO. 31 OF 11 AUGUST 2010

(Published in the Federal Official Gazette no. 154 of 12 August 2010)

Provides for the conduction of Pharmaceutical Equivalence and Comparative Dissolution Profile Studies.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency (Anvisa), in the use of the attributions vested in it under Article 11, item IV of the Regulation approved by Decree no. 3,029 of 16 April 1999, and considering item II and paragraphs 1 and 3 of Article 54 of the Internal Regulation approved in accordance with Annex I of Anvisa Ordinance no. 354 of 11 August 2006, republished in the Federal Official Gazette of 21 August 2006, as decided upon in a meeting held on 5 August 2006, adopts the following Resolution, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Article 1. This Resolution provides for the requirements to carry out Pharmaceutical Equivalence and Comparative Dissolution Profile Studies to be met by Pharmaceutical Equivalence Sites and Study Sponsors.

Article 2. Definitions:

I – Accessory: complement intended to dose, conduct, or carry out the administration of a dosage form to a patient. It is commercialized within the secondary package with the medicinal product and with no direct contact with the dosage form;

II – High Solubility: the active substance which amount corresponding to its highest posology dosage available in the Brazilian market is soluble in 250mL, or less, of aqueous medium in a scale of 1.2-6.8 pH, under a temperature of 37 ± 1ºC, is considered as highly soluble;

III – Pharmaceutical Equivalence Site: laboratory accredited by Anvisa, which carries out minimum physico-chemical assays and, when applicable, minimum microbiological or biological assays of Pharmaceutical Equivalence and Comparative Dissolution Profile Studies, of at least one of the dosage forms: solid, liquid, and semi-solid, being technical and legally responsible for the veracity of data and information from the studies in accordance with this Resolution, without prejudice to the Study Sponsor's attributions;

IV – Study Site: site contracted by the Study Sponsor, responsible for Pharmaceutical Equivalence and Comparative Dissolution Profile Studies;

V – Pharmaceutical Equivalence Certificate: document elaborated by the Pharmaceutical Equivalence Site, which attests results and provides conclusions regarding the Pharmaceutical Equivalence Study, excluding raw data;

VI – Comparative Dissolution Profile Certificate: document elaborated by the Pharmaceutical Equivalence Site, which attests results and provides conclusions regarding the Comparative Dissolution Profile Study, excluding raw data;

VII – Raw Data: every record and evidence resulting from original observations and activities of a certain study. They may include records of data, tables, chromatograms, spectra, photographs, hand-written data, electronic data, and others;

VIII – Very rapid dissolution: average dissolution of at least 85% of the active substance in up to 15 minutes;

IX – Rapid dissolution: average dissolution of at least 85% of the active substance in up to 30 minutes;

X – Information Assays: analytic assays required by individual monograph or by general methods of official compendia or also by norms and regulations approved/ endorsed by Anvisa, for which there is no specification defined, and the results of which should not be used for the purpose of comparison between Test Medicinal Products and Reference/ Comparator Medicinal Products in the Pharmaceutical Equivalence Study. For such studies, the test medicinal product must comply with its own specifications;

XI – Pharmaceutical Equivalence Study: set of physico-chemical and, when applicable, microbiological and biological assays evidencing that two medicinal products are Pharmaceutical Equivalents;

XII – Comparative Dissolution Profile Study: analytic method with collections at multiple points to assess the dissolution of a certain active substance comparing two formulations;

XIII – Pharmaceutical Equivalents: medicinal products with the same dosage form, the same administration route, and the same amount of the same active substance, that is, the same salt or ester of the therapeutic molecule, containing or not identical excipients, provided that they are well established for the intended function. Those medicinal products must comply with the same requirements of the individual monograph in the Brazilian Pharmacopoeia, preferably, or with other official compendia, specific norms or regulations approved/ endorsed by Anvisa, or, in the lack of such, they must comply with other quality and performance standards. Modified-release dosage forms requiring reservoir or excess may or may not contain the same amount of active substance, provided that they release identical amounts of the same active substance within the same dosage interval;

XIV – Dosage form: final state of presentation of pharmaceutical active ingredients after one or more pharmaceutical operations carried out with the addition of appropriate excipients or with no addition of excipients, in order to facilitate its use and achieve the desired therapeutic effect, with characteristics adequate to a certain administration route;

XV – Immediate-Release Dosage form: dosage form in which the total dose of the active substance is rapidly released after its administration. It generally presents an average dissolution of at least 75% of the active substance within 45 minutes during *in vitro* assays. Such dosage form may also present types of dissolutions characterized as rapid and very rapid;

XVI – Extended-Release Dosage Form: dosage form presenting modified release in which the active substance is gradually released form the dosage form for an extended period of time;

XVII – Delayed-Release Dosage Form: dosage form presenting modified release in which the active substance is released at a different time from immediately after its administration. Gastro-resistant preparations are considered as retarded-release form because they are intended to resist to the gastric fluid and release the active substance in the intestinal fluid;

XVIII – Comparator Medicinal Product: medicinal product submitted to a Comparative Dissolution Profile Study for the purpose of post-marketing authorization alterations to medicinal products, in accordance with specific legislation, which the Test Medicinal Product will be compared to;

XIX – Reference Medicinal Product: innovative medicinal product granted marketing authorization by the federal entity responsible for health surveillance and commercialized in Brazil, the efficacy, safety, and quality of which were scientifically evidenced to the competent federal entity in marketing authorization documents;

XX – Test Medicinal Product: medicinal product submitted to Pharmaceutical Equivalence and Comparative Dissolution Profile Studies;

XXI – Discriminative Dissolution Method: method able to evidence significant alterations in formulations and production processes of the tested medicinal products, which may affect formulation performance;

XXII – Study Sponsor: public or private legal entity that financially supports the Pharmaceutical Equivalence and Comparative Dissolution Profile Studies; being technically and legally co-responsible, with the Study Responsible Site, for the veracity of data and information from the studies;

XXIII – Pharmaceutical Equivalence Study Protocol: document elaborated by the Pharmaceutical Equivalence Site detailing how the Pharmaceutical Equivalence Study will be conducted;

XXIV – Comparative Dissolution Profile Study Protocol: document elaborated by the Pharmaceutical Equivalence Site detailing how the Comparative Dissolution Profile Study will be conducted;

XXV – Analytical Methods Partial Validation Protocol: document elaborated by the Pharmaceutical Equivalence Site detailing how the Analytical Methods Partial Validation will be conducted;

XXVI – Pharmaceutical Equivalence Study Report: document elaborated by the Pharmaceutical Equivalence Site attesting results of and providing conclusion on the Pharmaceutical Equivalence Study, including raw data;

XXVII – Comparative Dissolution Profile Study Report: document elaborated by the Pharmaceutical Equivalence Site attesting results of and providing conclusion on the Comparative Dissolution Profile Study, including raw data;

XXVIII – Analytical Methods Partial Validation Report: document elaborated by the Pharmaceutical Equivalence Site attesting results of and providing conclusion on the Analytical Methods Partial Validation, including raw data;

XXIX – Pharmacopoeial Reference Chemical Substances: substance or mixture of substances established and distributed by pharmacopoeias or official public institutions duly authorized, with a high degree of purity and uniformity. Such substances are intended to use in chemical and physical assays in which their proprieties are compared to those of the products under analysis;

XXX – Characterized Chemical Reference Substances: reference material not established by pharmacopoeias or official public institutions duly authorized, which must have a high degree of

purity and uniformity. It must be carefully analyzed regarding its identification, characterization, impurities, and quantitative analysis; and

CHAPTER II

PHARMACEUTICAL EQUIVALENCE STUDY

Section I

General Considerations on the Pharmaceutical Equivalence Study

Article 3. The Pharmaceutical Equivalence Study shall be carried out:

I – by the Pharmaceutical Equivalence Site duly accredited by Anvisa for this particular purpose, and prior to the Relative Bioavailability/ Bioequivalence Study, when applicable to the dosage form;

II – simultaneously comparing the Test Medicinal Product to the Reference Medicinal Product; and

III – with batches within their validity period.

Paragraph 1. Medicinal products already granted marketing authorization by Anvisa must be packaged in their commercial packages.

Paragraph 2. In case of studies with pilot batches, the medicinal products must be packaged at least in their primary package, duly identified according with the legislation in force, including its accessory, if applicable.

Paragraph 3. The Relative Bioavailability/ Bioequivalence Study, referred to in item I, must compulsorily use the same batches of the Test Medicinal Products and the Reference Medicinal Products used in the Pharmaceutical Equivalence Study.

Article 4. The Pharmaceutical Equivalence Study may be carried out with medicinal products presenting the dosage form of coated pill/ tablet, the Reference Medicinal Product of which is a non-coated pill or vice-versa, provided that the coating does not control the active substance release.

Article 5. In case of dosage forms administered in drops, the number of drops corresponding to 1mL must be determined, indicating the amount of active substance in each drop.

Sole Paragraph. The difference allowed regarding the number of drops determined by milliliter of the Test Medicinal Product is of up to around 10% in relation to the nominal value stated in the Reference Medicinal Product package insert.

Article 6. The Pharmaceutical Equivalence Study shall not be accepted if carried out with Test and Reference Medicinal Products packaged in primary packages intended to dose/ conduct/ execute the administration of their dosage forms or if they have accessories requiring specific different assays. Example: oral solution using measuring spoons, which do not require a drip assay, may not be compared to an oral solution that uses a drop dispenser, which requires a drip assay.

Article 7. In case of dosage forms exempted from Relative Bioavailability/ Bioequivalence Study, according to provisions set forth in specific standards and regulations approved/ endorsed by

Anvisa, the difference of content between the Test Medicinal Product and the Reference Medicinal Product may exceed 5%, provided that both medicinal products are within the specification of the analytical method adopted.

Article 8. In case of dosage forms not exempted from Relative Bioavailability/ Bioequivalence Study, the difference in content of active substance between the Test Medicinal Product and the Reference Medicinal Product is recommended to not exceed 5%.

Section II

Criteria to Conduct the Pharmaceutical Equivalence Study

Article 9. Test Medicinal Products and Reference Medicinal Products shall fully comply with all requirements of the Brazilian Pharmacopoeia individual monograph, preferably, or with the ones of other official compendia, specific standards or regulations approved/ endorsed by Anvisa, when applicable, complemented with assays described in general methods of the Brazilian Pharmacopoeia and other official compendia regarding the dosage form being tested.

Article 10. In the absence of a monograph described in official compendia, specific standards or regulations approved/ endorsed by Anvisa, an analytical method validated by the Study Sponsor or the Pharmaceutical Equivalence Site must be used.

Paragraph 1. In the case referred to in the caption of this article, the Pharmaceutical Equivalence Study must be complemented with assays described in general methods of the Brazilian Pharmacopoeia and other official compendia, specific standards or regulations approved/ endorsed by Anvisa, for the dosage form being tested.

Paragraph 2. Test Medicinal Products and Reference Medicinal Products must comply with the same specifications, and the results from non-informative assays of the Test Medicinal Product must be compared to those of the Reference Medicinal Product.

Article 11. When the analytical method is transferred by the Study Sponsor, the Pharmaceutical Equivalence Site must carry out a partial validation of this method prior to the Pharmaceutical Equivalence Study.

Article 12. Pharmaceutical Equivalence Studies using methods and specifications of monographs from several official compendia for the same study are not accepted.

Sole Paragraph. When the Brazilian Pharmacopoeia or other official compendium presents a monograph for a certain medicinal product, which does not comprise all assays required to evidence pharmaceutical equivalence, the study must be complemented by assays of another official compendium, standards or regulations approved/ endorsed by Anvisa, or other applicable quality standards using a validated method.

Article 13. For the purposes of pharmaceutical equivalence, the following are considered informative assays:

I – aspect;

II – viscosity;

III – density;

IV – average weight value; or

V – average volume value.

Paragraph 1. Variations of average weight and average volume for each medicinal product tested are not informative and pharmacopoeial specifications must be complied with.

Paragraph 2. The assays referred to in this article are not considered informative assays when they are important to determine quality, safety, and efficacy of medicinal products or present specifications described in official compendia, standards or regulations approved/ endorsed by Anvisa.

Article 14. In the absence of a dissolution method described in an official compendium, specific standards or regulations approved/ endorsed by Anvisa, the Study Sponsor is responsible for the report regarding development and validation of the dissolution method that must be used according to provisions in Brazilian and international guidelines, and such report must include data confirming that the method is discriminative.

I – the Study Site must file a copy of the dissolution method development and validation report provided by the Study Sponsor;

II – the Study Site must carry out a partial validation of the dissolution method developed and transferred by the Study Sponsor; and

III – the dissolution method development report must include at least the following information:

a) quantitative solubility assessment of the active substance within physiological pH range (1.2 to 6.8), considering temperature of 37°C ± 1°C, according to the phase diagram method for the solubility analysis, for example. The assessment requires increasing quantities of the active substance to be tested in a fixed volume of, at least, three different media, for instance, at pH 1.2, 4.5, and 6.8;

b) confirmation that the dissolution medium is the most adequate media to the active substance in the study dosage form. The confirmation requires investigation of dissolution curves within physiological pH range (1.2 to 6.8), such as, for example, at pH 1.2, 4.5, and 6.8, considering temperature of 37°C ± 1°C;

c) confirmation that the apparatus, rotation, and filters used in the sample collection procedure are the most adequate ones to the active substance and the study dosage form;

d) rationale for the need to use anchors, when applicable;

e) evidence of the need to use surfactants, as well as the quantity used, when applicable;

f) confirmation of and rationale for the selection of Q value (quantity of the active substance dissolved expressed as a percentage of the labeled value of the unit dosage); and

g) rationale for the need to apply a deaeration method, when applicable.

Paragraph 1. The report on the dissolution method development may also be adopted when the dissolution method described in an official compendium, specific standards, or regulations approved/ endorsed by Anvisa, is not adequate to the product, provided it is duly confirmed.

Paragraph 2. Dissolution medium pH must be within the physiologic range (1.2 to 6.8). If it is necessary to use a different pH range, it must be justified in the dissolution method development report.

Paragraph 3. The Study Sponsor may contract a Pharmaceutical Equivalence Site accredited by Anvisa for development and validation of the dissolution method.

Article 15. The Pharmaceutical Equivalence Study for nasal and pulmonary sprays and aerosols must be carried out in accordance with official compendia, specific standards, or regulations approved/ endorsed by Anvisa.

Article 16. For sprays and aerosols of administration routes not referred to in Article 15, pharmacopoeial assays must be conducted for the dosage form at issue. For example: for spray solutions of dermatological administration route, all assays of the individual monograph of and general methods set forth for the solution pharmaceutical form must be carried out.

Sole Paragraph. When medicinal products referred to in the caption of this article have their dosage defined in their posology, the active substance concentration per dosage must also be confirmed.

CHAPTER III

COMPARATIVE DISSOLUTION PROFILE STUDY

Section I

General Considerations on the Comparative Dissolution Profile Study

Article 17. The Comparative Dissolution Profile Study must be carried out in the following conditions:

I – by a Pharmaceutical Equivalence Site duly accredited by Anvisa for this particular purpose and prior to the Relative Bioavailability/ Bioequivalence Study, when applicable;

II – using the same dissolution method used in the Pharmaceutical Equivalence Study, when applicable;

III – using the same batches of the Test Medicinal Product and Reference Medicinal Product used in the Pharmaceutical Equivalence Study and the Relative Bioavailability/ Bioequivalence Study, when applicable;

IV – simultaneously with the Test Medicinal Product and Reference/ Comparator Medicinal Product; and

V – with batches within their validity period.

Paragraph 1. Medicinal products already granted marketing authorization by Anvisa must be packaged in their commercial packages.

Paragraph 2. In case of studies carried out in pilot batches, the medicinal products must be packaged at least in their primary package, duly identified according to the legislation in force.

Paragraph 3. In post-marketing authorization cases, in which a Pharmaceutical Equivalence Study is not applicable, the Comparative Dissolution Profile Study must be conducted using the dissolution method described in the Brazilian Pharmacopoeia, preferably, or in other official compendia, specific standards, or regulations approved/ endorsed by Anvisa. In the absence of a monograph published in an official compendium, specific standards, or regulations approved/

endorsed by Anvisa, the company must comply with the criteria set forth in Article 14 of this Resolution.

Article 18. For extended-release dosage forms, sample collection must represent the dissolution process, for instance, at 1, 2, and 4 hours and subsequently every two hours until both medicinal products present 80% dissolution of the active substance, or the plateau is achieved.

Article 19. For delayed-release dosage forms, dissolution in HCl 0.1N medium must be carried out for 2 hours (acid stage), followed by dissolution in buffer medium. After the medicinal product is placed in the buffer medium, sample collection shall be representative of the dissolution process, for instance, at 15, 30, 45, 60, and 120 minutes until both medicinal products present 80% dissolution of the active substance, or the plateau is achieved.

Article 20. The Comparative Dissolution Profile Study may be conducted with medicinal products presented in the form of coated pill/ tablet, the Reference/ Comparator Medicinal Product of which is a simple pill or vice-versa, provided that the coating does not control the active substance release mechanism.

Article 21. When the result of the Comparative Dissolution Profile Study is not similar, evidence of therapeutic equivalence between the Test Medicinal Product and the Reference/ Comparator Medicinal Product may be based on the result of the Relative Bioavailability/ Bioequivalence Study, at ANVISA's discretion.

Article 22. The Comparative Dissolution Profile Study is not applicable for the following dosage forms:

I – powder, granulate, and effervescent dosage forms that, when reconstituted, become solutions;

II – semi-solid, except for suppository;

III – dosage forms administered as immediate-release nasal or pulmonary sprays or aerosols;

IV – gases; or

V – liquids, except for suspensions.

Paragraph 1. For the dosage forms referred to, when there is a dissolution methodology described in an official compendium, specific standards, or regulations approved/ endorsed by Anvisa, the Comparative Dissolution Profile Study or complementary assay must be carried out, at Anvisa's discretion.

Paragraph 2. For the dosage forms not referred to, the Comparative Dissolution Profile Study must be carried out.

Section II

Comparison of Dissolution Profiles

Article 23. The comparison of Dissolution Profiles is useful when it is desired to know the behavior of two medicinal products before submitting them to a Relative Bioavailability/ Bioequivalence Study, to exempt lower dosages of such studies and for post-marketing authorization alterations.

Article 24. In this comparison the curve is evaluated as a whole, using the Simple Independent Model Method.

I – a Simple Independent Model Method applies a difference factor (F1) and a similarity factor (F2). Pursuant to this Resolution, comparative dissolution profiles are evaluated just using the similarity factor (F2) calculation; and

II – the factor F2 corresponds to a similarity measurement between the percentages dissolved for both profiles:

$$F2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0,5} \times 100\right\}$$

where n = number of collection times considered for the purpose of F2 calculation;

Rt = value of the percentage dissolved in time t, obtained with the Reference or Comparator Medicinal Product;

Tt = value of the percentage dissolved from the Tested Medicinal Product or the altered formulation, in time t.

Sole Paragraph. The similarity factor (F2) shall only be calculated when the dissolution assay conditions are exactly the same applied to evaluate the Tested Medicinal Product and the Reference/ Comparator Medicinal Product.

Subsection I

Dissolution Profiles Comparison Procedure

Article 25. The comparison of dissolution profiles must be in accordance with the following procedures:

I – apply twelve units of the Test Medicinal Product and twelve units of the Reference/ Comparator Medicinal Product; and

II – calculate factor F2 using the equation presented in item II of Article 24.

Article 26. In order to both dissolution profiles to be considered similar, they must meet the following criteria:

I – [REVOKED]

II – the similarity factor (F2) value must be within 50 to 100;

III – collection times must be the same for both formulations;

IV – the number of collection points must be representative of the dissolution process until plateau is achieved on the curve, and it is mandatory to quantify samples of, at least, five collection times;

V – for the purpose of F2 calculation, use at least the first three points, excluding time zero;

VI – for the purpose of F2 calculation, include only one curve point after both medicinal products have reached the average of 85% dissolution; and

VII – In order to allow the use of averages, variation coefficients for the first collection points must not exceed 20%. For all other points, it is considered a maximum of 10%. The amount corresponding to 40% of total collection points is considered as the first collection points. For example, for a dissolution profile with five collection times, the first two collection points are considered as first points.

Sole Paragraph. When the active substance presents high solubility and the formulation is of immediate release, presenting very rapid dissolution for both medicinal products, the F2 factor loses its discriminative power and, therefore, it is not necessary to be calculated. In these cases, the very rapid dissolution of the products must be confirmed through the curve graph, collecting, for instance, at 5, 10, 15, 20, and 30 minutes. The variation coefficient at the point of 15 minutes cannot exceed 10%.

CHAPTER IV

SAMPLES TO CARRY OUT PHARMACEUTICAL EQUIVALENCE AND COMPARATIVE DISSOLUTION PROFILE STUDIES

Article 27. The quantity of samples to be obtained by the Site must enable a complete Pharmaceutical Equivalence and Comparative Dissolution Profile Study and a retest.

Paragraph 1. The period to retain the batches must correspond to at least one year after the expiration date of the latest medicinal product to expire.

Paragraph 2. For sterile dosage forms, it is mandatory to carry out sterility and bacterial endotoxin assays or pyrogen testing assay in the Pharmaceutical Equivalence Study, for both Test and Reference/ Comparator Medicinal Products. Retention samples related to such assays shall be waived for the Reference/ Comparator Medicinal Product.

CHAPTER V

REFERENCE CHEMICAL SUBSTANCES TO CONDUCT PHARMACEUTICAL EQUIVALENCE AND COMPARATIVE DISSOLUTION PROFILE STUDIES

Article 28. A Reference Chemical Substance made official by the Brazilian Pharmacopoeia, preferably, or by other official compendia, must be used.

Article 29. If the Reference Chemical Substance does not exist, the use of a Work Chemical Substance is allowed, provided that the following are duly determined: identity, content, impurity quantitative profile and, when applicable, impurity qualitative profile and other specific assays.

Paragraph 1. The Study Sponsor or the Study Site is responsible for assuring Work Chemical Substance data reliability through a critical analysis of its analytical report.

Paragraph 2. The Work Chemical Substance expiration date must meet the raw material validity period determined by its manufacturer. The Study Sponsor and/ or the Pharmaceutical Equivalence Site are not allowed to revalidate the raw material aiming at extending the Work Chemical Substance validity period.

CHAPTER VIII

CERTIFICATES OF PHARMACEUTICAL EQUIVALENCE AND COMPARATIVE DISSOLUTION PROFILE STUDIES

Article 30. The Pharmaceutical Equivalence Study Certificate must meet the following criteria:

I – when there are quantifiable specifications, the assay results must be described as numerical quantities in units established by official compendia or the International System of Units. Results described as “conform”, “compliant”, or others shall not be accepted;

II – for the sterility assay, the result description shall only be accepted as “sterile” or “nonsterile”;

III – in assays for dissolution, disintegration, average weight, average volume, hardness, and uniformity of unit dosages, the following must be informed: average, minimum and maximum results and, when applicable, variation relative/ limit standard deviation for both Test and Reference/ Comparator Medicinal Products;

IV – aspect assay results must describe the characteristics of Test and Reference/ Comparator Medicinal Products, such as: form, dimension, color, presence of ridges, presence of coating, inscriptions, characteristic odor, or other characteristics enabling to identify the samples;

V – for methodologies described in official compendia, the “Bibliographic References” field of the Certificate must refer to the compendium adopted with at least its year, issue, edition, and page. When the compendium used is electronic, page number is not necessary; and

VI – for methodologies not described in official compendia, the “Bibliographic References” field of the Certificate must refer to the identification code of the analytical method adopted, as well as the identification code of the respective Validation Report.

Article 31. The Comparative Dissolution Profile Study Certificate must meet the following criteria:

I – in the field “Quantification Method Specification”, in addition to method specifications, the assay acceptance criteria must be reported;

II – for methodologies described in official compendia, the “Bibliographic References” field of the Certificate must refer to the compendium adopted with at least its year, issue, edition, and page. When the compendium used is electronic, page number is not necessary; and

III – for methodologies not described in official compendia, the “Bibliographic References” field of the Certificate must refer to the identification code of the analytical method adopted, as well as the identification code of the respective Validation Report.

CHAPTER IX

FINAL PROVISIONS

Article 32. The Study Sponsor must send to Anvisa the Pharmaceutical Equivalence and Comparative Dissolution Profile Study Certificate, according to the models available on Anvisa website.

Article 33. The Protocols and Reports of the Studies of Pharmaceutical Equivalence, Comparative Dissolution Profile, Analytical Method Validation and Partial Validation, as well as raw data and statistical data related to the evaluation of every assay with the Test and Reference/ Comparator Medicinal Products must be available to Anvisa and the Study Sponsor.

Sole Paragraph. The Study Site is responsible for filing all documentation referred to in the caption of this article.

Article 34. Additional documentations and assays may be requested at any time by Anvisa with the purpose of complementing the assessment of Pharmaceutical Equivalence, Comparative Dissolution Profile, Analytical Method Validation and Partial Validation Studies.

Article 35. Pharmaceutical Equivalence Sites must comply with technical standards and regulations in force.

Article 36. This Resolution shall enter into force 60 days after its official publication.

Article 37. Resolution-RE No. 310 of 1 September 2004 is hereby revoked.

DIRCEU RAPOSO DE MELLO