

COLLEGIATE BOARD RESOLUTION – RDC NO. 753 OF 28 SEPTEMBER 2022

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Provides for the marketing authorization for medicinal products for human use with synthetic and semi-synthetic active ingredients, classified as new, innovative, generic, and similar medicinal products.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and Article 187, item VI, Paragraphs 1 of the Internal Regulation approved in the terms of Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 28 September 2022, and I, Director-President, determine its publication:

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and Scope

Article 1. This Resolution establishes the criteria and the minimum necessary documentation for the grant of marketing authorization for medicinal products for human use with synthetic and semi-synthetic active ingredients, aiming at ensuring the quality, safety, and efficacy of such medicinal products.

Article 2. This Resolution applies to applications for the marketing authorization for medicinal products classified as new, innovative, generic, and similar medicinal products, except for those ruled by specific legislation in force.

Section II

Definitions

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

I – accessory: complement intended to dose, conduct, or execute the administration of the pharmaceutical form to the patient, commercialized inside the secondary package, with the medicinal product and without direct contact with the pharmaceutical form;

II – fixed-dose combination: fixed ratio of doses of two or more active pharmaceutical ingredients in the same pharmacotechnical unit;

III – kit combination: fixed ratio of doses of two or more active pharmaceutical ingredients in different pharmacotechnical units, in the same commercial presentation, for concomitant or sequential use;

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

V – relative bioavailability: comparison of the bioavailability of two products under the same experimental design;

VI – bioequivalence: demonstration of bioavailability levels equivalent between products, when studied under the same experimental design;

VII – biobatch: batch used in the conduction of clinical studies presented to confirm safety and efficacy or in studies to prove pharmaceutical equivalence or bioequivalence;

VIII – Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA, in Portuguese): administrative instrument that certifies the adequacy of the Active Pharmaceutical Ingredient Dossier (DIFA, in Portuguese);

IX – Good Manufacturing Practices Certificate (CBPF, in Portuguese): document issued by Anvisa certifying that a given establishment complies with the Good Manufacturing Practices as provided for in the health legislation in force, which is required for the commercialization of the product;

X – API basic structural class: basic chemical structure of the API that confers pharmacological activity or other direct effect on the diagnosis, cure, treatment, or prevention of a disease, and it may also affect the structure and function of the human organism;

XI – ATC Code (Anatomical Therapeutic Chemical): acronym used for the Anatomical Therapeutic Chemical classification of pharmaceuticals in different groups and sub-groups, according to the organ or system on which they act and according to their chemical, pharmacological, and therapeutic properties;

XII – serious debilitating condition: disease or condition associated with irreversible morbidity or high probability of death, unless the course of the disease is interrupted;

XIII – quality control: set of measures aimed at ensuring, at any time, the production of batches of medicinal products that meet the standards of activity, purity, efficacy, and innocuity (Law no. 6,360 of 23 September 1976);

XIV – technical data: protocols, guides, monographs, authorizations, votes, letters, certificates, declarations, reports, or technical opinions issued by national or international entities containing information on the safety and efficacy of the medicinal product or API, including real-life evidence;

XV – Brazilian Common Denomination (DCB, in Portuguese): name of the pharmaceutical or pharmacologically active ingredient approved by Anvisa (Law no. 6,360 of 23 September 1976);

XVI – emerging or re-emerging disease: a new health condition, usually of infectious origin, or a previously known condition that acquires or regains epidemiological significance in public health;

XVII – neglected disease: disease that is not economically attractive for the development of medicinal products, or because it affects a population predominantly in developing countries;

XVIII – Active Pharmaceutical Ingredient Dossier (DIFA, in Portuguese): set of administrative and technical documents of an active pharmaceutical ingredient;

XIX – package: wrap, recipient, or any form of packaging, either removable or not, intended to cover, package, fill, protect, or keep, either specifically or not, medicinal products;

XX – primary package: package that keeps direct contact with the medicinal product;

XXI – secondary package: external package of the product, which is in contact with the primary package or intermediate wrap, and may contain one or more primary packages;

XXII – functional secondary package: package that provides additional protection or serves to release the dose of the product;

XXIII – public health emergency: situation that demands the urgent use of measures to prevent, control, and contain risks, damage, and harm to public health, declared in situations that can be epidemiological (outbreaks and epidemics), of disasters, or of non-assistance to the population;

XXIV – intermediate wrap: optional package that is in contact with the primary package and constitutes a wrap or any other form of removable protection, and may contain one or more primary packages;

XXV – pharmaceutical equivalence study: set of physical-chemical and, when applicable, microbiological and biological trials that prove that two medicinal products are pharmaceutical equivalents;

XXVI – bridging study: study conducted for the purpose of establishing correlation between medicinal products or populations in order to allow extrapolation of efficacy and safety data;

XXVII – pharmaceutical equivalents: medicinal products that have the same pharmaceutical form, the same route of administration, and the same quantity of the same active substance, that is, the same salt or ester of the therapeutic molecule, which may or may not contain identical excipients, provided that they are well established for the intended function;

XXVIII – current commercialization experience: post-marketing data or information on the proposed medicinal product or API, currently commercialized abroad, regarding its use, therapeutic effects, and safety profile, according to the conditions of the current marketing authorization in the country where it is commercialized;

XXIX – proportional formulations: formulations of medicinal products in which all formulation components are exactly in the same proportion in all different dosages or the ratio between the excipients and the total weight of the formulation is within the limits for moderate alteration of excipients, as established in the specific legislation in force for the post-marketing authorization of medicinal products;

XXX – Active Pharmaceutical Ingredient (API): any substance introduced in the formulation of a pharmaceutical form that, when administered in a patient, acts and an active ingredient. Such substances may perform a pharmacological activity or another direct effect on the diagnosis, cure, treatment, or prevention of a disease, which may also affect the structure and operation of the human body;

XXXI – analogous Active Pharmaceutical Ingredient (API): API with a basic structural class common to another API in which one or more atoms or functional groups have been substituted, including free bases, salts, esters, ethers, isomers, complexes, and other derivatives;

XXXII – scientific literature: meta-analyses, systematic reviews, or scientific articles published in an indexed journal containing information regarding the safety and efficacy of the medicinal product or API;

XXXIII – batch: defined quantity of raw material, packaging material, or product processed in one or more processes, the essential characteristic of which is homogeneity. In order to complete certain manufacture stages, it may be necessary to divide a batch in several sub-batches, which will then be grouped to form a homogeneous final batch. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by the intended homogeneity;

XXXIV – pilot batch: batch of pharmaceutical product manufactured through a process representing and reproducing an industrial scale production batch;

XXXV – raw materials: active or inactive substances that are used in the manufacture of medicinal products, both those remaining unaltered and those likely to undergo alterations (Law no. 6,360 of 23 September 1976);

XXXVI – medicinal product: pharmaceutical product, technically obtained or developed, for prophylactic, curative, palliative, or diagnosis purposes (Law no. 5,991 of 17 December 1973);

XXXVII – reference medicinal product: innovative product authorized by Anvisa and commercialized in Brazil, the efficacy, safety, and quality of which have been scientifically proven to Anvisa, at the time of marketing authorization;

XXXVIII – generic medicinal product: a medicinal product similar to a reference or innovative product, which intends to be interchangeable with it, generally produced after the expiration or waiver of patent protection or other exclusivity rights, having its efficacy, safety, and quality proven, and designated by the DCB or, in the absence thereof, by the INN (Law no. 6,360 of 23 September 1976);

XXXIX – innovative medicinal product: medicinal product with a new association, new monopharmaceutical, new route of administration, new concentration, new pharmaceutical form, new packaging, new therapeutic indication, or with a different innovation related to a new medicinal product already granted marketing authorization in Brazil;

XL – new medicinal product: medicinal product containing a new molecule and complying with the provisions set forth in Law no. 9,279 of 14 May 1996;

XLI – similar medicinal product: product that contains the same active ingredient(s), presents the same concentration, pharmaceutical form, route of administration, dosage, and therapeutic indication, and which is equivalent to the medicinal product granted marketing authorization by Anvisa, which may differ only in characteristics related to size and shape of the product, expiration date, package, labeling, excipients, and vehicles, having its effectiveness, safety and quality been proven, and it must always be identified by commercial name or brand name;

XLII – new molecule: new Active Pharmaceutical ingredient (API) or analogous API considered as a new chemical entity in Brazil;

XLIII – batch number: designation printed on the label of a medicinal product and products covered by Law no. 6,360 of 23 September 1976, which allows to identify the batch or the parcel they belong to and, if necessary, locate and review all manufacturing and inspection operations carried out during production (Law no. 6,360 of 23 September 1976);

XLIV – bulk product: any product that has completed all processing stages up to, but not including, primary packaging, and sterile products in their primary packaging are considered bulk products;

XLV – finished product: a product that has undergone all production stages, including labeling and final packaging;

XLVI – intermediate product: partially processed product that must undergo subsequent manufacturing stages before becoming a bulk product.

Paragraph 1. The pharmaceutical equivalent medicinal products provided for in item XXVII of this article must comply with the same requirements of the individual monograph of the Brazilian Pharmacopoeia, preferably, or with those of other official compendia, specific standards or regulations approved/ endorsed by Anvisa or, in their absence, with other quality and performance standards.

Paragraph 2. The pharmaceutical equivalent medicinal products provided for in item XXVII of this article whose pharmaceutical forms are of modified release that require reservoir or excess may or may not contain the same amount of the active substance, as long as they release identical amounts of the same active substance in the same dosage interval.

CHAPTER II

GENERAL PROVISIONS

Article 4. The documentation must be accompanied by the documents required in this Resolution and in the checklist established for each application subject, and it must be submitted in accordance with the specific legislation in force.

Paragraph 1. The documentation submitted in printed copies must have its pages numbered.

Paragraph 2. The documentation presented electronically must contain files that allow text search, copying, bookmarks, and hyperlinks that facilitate navigation.

Paragraph 3. For new and innovative medicinal products, the subject of the application to be submitted is provided for in Normative Instruction – IN no. 184 of 28 September 2022, which defines the subjects for the administrative submission of the applications for marketing authorization for synthetic and semi-synthetic medicinal products classified as new and innovative medicinal products, and its updates.

Paragraph 4. The official documents in a foreign language used for the purposes of marketing authorization must be accompanied by a sworn translation in accordance with the legislation, except those presented in English or Spanish, in accordance with Collegiate Board Resolution – RDC no. 25 of 16 June 2011, and its updates.

Article 5. For the purposes of the provisions in this Resolution, if there are specific legislation or guides, these must also be complied with, and the respective evidence must be presented.

Article 6. The medicinal product to be granted marketing authorization must be classified as one of the following regulatory categories:

I – New medicinal product;

II – Innovative medicinal product;

III – Generic medicinal product; or

IV – Similar medicinal product.

Article 7. New, innovative, and similar medicinal products must have a commercial name, in accordance with Collegiate Board Resolution – RDC no. 59 of 10 October 2014, and its updates.

Article 8. Generic medicinal products must adopt the nomenclature contained in the Brazilian Common Denomination (DCB) list, in accordance with Collegiate Board Resolution – RDC no. 469 of 23 February 2021, and its updates.

Article 9. The presentations of the medicinal product to be granted marketing authorization must be coherent with the dosage regimen and the intended therapeutic indication.

Article 10. The applicant for marketing authorization is responsible for the quality of the API used in the manufacture of the medicinal product.

CHAPTER III

GENERAL REQUIREMENTS FOR MARKETING AUTHORIZATION

Section I

Measures Prior to Marketing Authorization

Article 11. Clinical trials of medicinal products for the purposes of marketing authorization must be planned, conducted, and monitored according to the Good Clinical Practices (GCP) guidelines.

Sole paragraph. Clinical trials of medicinal products conducted, in whole or partially, in Brazil for the purposes of medicinal product marketing authorization must comply with the provisions of Collegiate Board Resolution – RDC no. 9 of 20 February 2015, and its updates.

Article 12. The applicant for marketing authorization must request the Brazilian Pharmacopoeia to include the API and excipients in the DCB list, in case they are not yet present in such list.

Article 13. When necessary, a hearing may be requested, or a protocol may be submitted to discuss the development path, the most appropriate classification, or the evidence of safety, efficacy, and quality prior to the marketing authorization application.

Sole paragraph. The procedures defined in the discussions prior to the marketing authorization application provided for in the caption of this article do not guarantee the marketing authorization for the proposed medicinal product, which shall only be granted upon analysis

and approval of the results of the study(ies) and other technical and legal requirements provided for in the specific legislation in force.

Section II

Administrative Documentation

Article 14. The application for marketing authorization for a medicinal product pursuant to this Resolution must be individualized per each pharmaceutical form.

Paragraph 1. For generic and similar medicinal products in which different concentrations for the same pharmaceutical form have different reference medicinal products elected, the application regarding all concentrations must be submitted in a single process.

Paragraph 2. An application for marketing authorization for a new or innovative medicinal product containing different pharmaceutical forms in the same commercial presentation may be accepted upon demonstration of a scientifically based clinical rationale.

Article 15. All applications submitted must be accompanied by the following documents:

I – application forms, FP1 and FP2, duly completed and signed;

II – proof of payment of the Health Surveillance Inspection Fee (TFVS, in Portuguese) and the respective Federal Collection Slip (GRU, in Portuguese), or exemption, when applicable, according to Collegiate Board Resolution – RDC no. 222 of 28 December 2006, and its updates;

III – model of the package insert text, according to the Collegiate Board Resolution – RDC no. 47 of 8 September 2009, and its updates;

IV – layout of primary and secondary packages of each presentation of the medicinal product, according to the Collegiate Board Resolution – RDC no. 71 of 22 December 2009, and its updates;

V – valid Good Manufacturing Practices Certificate – GMPC issued by Anvisa, for the production line in which the medicinal product, object of marketing authorization, will be manufactured, or a copy of the inspection request protocol for the purposes of issuance of the GMPC, in accordance with Collegiate Board Resolution – RDC no. 497 of 20 May 2021, and its updates;

VI – Technical Report (TR);

VII – history of interactions with Anvisa during the stage prior to marketing authorization (hearings, meetings, communications through service channels, responses to protocols), in chronological order, including:

a) any commitments the company has made to Anvisa, mentioning the location of the fulfillment of each commitment in the dossier;

b) copies of the records of the interactions; and

c) interactions with other entities that are deemed relevant by the applicant for the analysis of the marketing authorization.

Paragraph 1. In addition to the documents listed in the caption of this article, in the case of imported products, the following must also be presented:

I – Certificate of Medicinal Product Marketing Authorization, or equivalent document, from the country of origin or, in its absence, from the country where the medicinal product is commercialized;

II – Regulatory status of the medicinal product in other countries, containing a list of those in which it is authorized and its respective status, including any commitments made to other regulatory authorities regarding the submission of additional data on quality, safety, efficacy, clinical pharmacology, or non-clinical toxicology; and

III – information regarding the stage of the medicinal product to be imported (finished product, bulk product, or product in primary packaging).

Paragraph 2. For intermediate products, a document confirming the good manufacturing practices issued by Anvisa or the body responsible for Health Surveillance in the manufacturing country may be presented.

Paragraph 3. The absence of a valid Certificate of Medicinal Product Marketing Authorization or GMPC does not hinder the submission of the marketing authorization application, but prevents its approval.

Paragraph 4. For the purposes of compliance with the provisions in item I of Paragraph 1 of this article, a medicinal product is considered as a pharmaceutical product, technically obtained or elaborated, in the same pharmaceutical form, route of administration, and concentration within the therapeutic range applied for marketing authorization in Brazil.

Section III

Technical Quality Documentation

Subsection I

Active Pharmaceutical Ingredient

Article 16. When submitting the application for marketing authorization for a medicinal product, the marketing authorization applicant must present the following information regarding the API:

I – letter from the holder of the Active Pharmaceutical Ingredient Dossier (DIFA), on behalf of the medicinal product marketing authorization applicant and with the DIFA reference number, authorizing the use of the DIFA as part of the analysis of the medicinal product subject of the marketing authorization application;

II – statement signed by the technical responsible or designated person attesting that the API manufacture is conducted in accordance with the Good Manufacturing Practices for APIs, from the introduction of starting materials;

III – number of the file of the API GMPC request, according to Collegiate Board Resolution – RDC that provides for the certification of good manufacturing practices for APIs;

IV – when there is a DIFA confidentiality restriction, statement from the technical responsible person of the marketing authorization applicant, or person designated by the company, that the marketing authorization applicant has possession of the open part;

V – for sterile API, description and validation of the API sterilization process, when not performed under the responsibility of the DIFA holder; and

VI – description of the physical steps (micronization, grinding, sieving, lyophilization), when not performed under the responsibility of the DIFA holder.

Paragraph 1. The marketing authorization applicant is responsible for assessing the adequacy of the API specification to the maximum daily dose, route of administration, and pharmaceutical form of the medicinal product object of marketing authorization.

Paragraph 2. Granting of the medicinal product marketing authorization shall be conditioned to valid API GMP certificate and CADIFA.

Paragraph 3. If the DIFA holder already has a CADIFA, the marketing authorization applicant must submit, in place of the documentation of item I, a copy of the CADIFA, with the declaration of access completed by the DIFA holder on behalf of the medicinal product marketing authorization applicant.

Paragraph 4. For APIs that do not fit the scope of the Collegiate Board Resolution – RDC establishing the DIFA and the CADIFA, the documentation required in the specific regulation in force must be submitted, as applicable, replacing the documents requested in the caption of this article.

Paragraph 5. For the purposes of the provisions in item II in the caption of this article, the statement must be based on a Good Manufacturing Practices audit conducted under the terms of the Collegiate Board Resolution – RDC that provides for the general guidelines for good manufacturing practices for medicinal products.

Subsection II

Medicinal Product

Article 17. When submitting a medicinal product marketing authorization application, the marketing authorization applicant must submit a technical report containing the following information:

I – on formulation development:

a) summary on the formulation development, considering the route of administration and use, as well as the packaging system;

b) information on the API compatibility with the excipients, key physicochemical characteristics of the API that may influence the performance of the finished product;

c) documents containing the details of manufacture, characterization, and controls with bibliographic reference to support the safety data for excipients used for the first time in a medicinal product or in a new route of administration;

d) data and discussion on the effectiveness assessment of the preservative system used in the formulation; and

e) justification in case of excess active ingredient.

II – on the finished product:

a) detailed description of the complete formula, naming the components according to the Brazilian Common Denomination (DCB, in Portuguese);

b) information on the quantity of each component of the formula and their respective functions, including capsule components, and indication of the respective quality specification references described in the Brazilian Pharmacopoeia or other official codes authorized by the specific legislation in force;

c) detailed description of the qualitative and quantitative proportion of the intermediate products used in the formula of the finished product; and

d) justification regarding the presence of a groove on the tablet with the appropriate tests.

III – on the production of the finished product:

a) production dossier related to 1 (one) batch;

b) name and responsibility of each manufacturer including subcontracted companies and each proposed manufacturing site involved in the production and tests to be carried out, including quality control and accelerated and long-term stability studies;

c) flowchart with the manufacturing process stages showing where materials enter the process, identifying process critical points and control points, intermediate tests, and control of the final product;

d) information on batch sizes of the finished product, description of the manufacturing process stages, including all parameters used, in-process control, and intermediate products;

e) list of the equipment involved in production, identified by operating principle (class) and design (subclass) with the respective capacities;

f) control of the critical stages with information about the tests and acceptance criteria carried out at the critical points identified in the manufacturing process, in addition to in-process controls; and

g) summary report of the manufacturing process validation, including batches, definition of the critical manufacturing stages with the respective justifications, parameters assessed, and indication of the results obtained and conclusion.

IV – on the quality control of raw materials:

a) specifications, analytical methods, and analytical report for the excipients, accompanied by bibliographic reference, made by the medicinal product manufacturer;

b) additional information for excipients of animal origin according to the specific legislation in force on the control of Transmissible Spongiform Encephalopathy; and

c) specifications, analytical methods and analytical report for the active pharmaceutical ingredient, accompanied by bibliographic reference, carried out by the medicinal product manufacturer.

V – on the quality control of the finished product:

a) specifications, analytical methods, and analysis report, accompanied by bibliographic reference, including analytical method validation reports; and

b) dissolution profile chart, where applicable.

VI – on primary packaging and functional secondary packaging:

a) description of the packaging material; and

b) report with specifications, analytical method, and results of the packaging quality control.

VII – on the intermediate wrap: description of the constitution material of the intermediate wrap and its specifications;

VIII – on the accessories accompanying the medicinal product in its commercial packaging: description of the accessory composition material and its specifications; and

IX – on the stability studies of the finished product:

a) report with the results of the accelerated and long-term stability studies conducted with three (3) batches, protocols used, including conclusions regarding conservation care and shelf life;

b) results of stability studies for medicinal products that, once opened or prepared, may undergo alterations in their original shelf life or original conservation care; and

c) results of the photostability study or technical justification for study exemption.

Paragraph 1. In compliance with subitem (b) of item I of the caption of this article, in the hypothesis of associations, a discussion must be presented on the compatibility among the active ingredients, as well as among them and the excipients.

Paragraph 2. In compliance with item I of the caption of this article, for generic and similar medicinal products, the dissolution method development report must be submitted, in accordance with the specific legislation in force.

Paragraph 3. In compliance with subitem "a" of item II of the caption of this article, in the absence of the DCB for any excipient used in the formulation, submit the requesting protocol for inclusion in the DCB list or the justification of absence issued by the Brazilian Pharmacopoeia.

Paragraph 4. The information explained in items II and III of the caption of this article and their subitems must be presented as set forth in Annex I of this Resolution.

Paragraph 5. In compliance with subitem "a" of item III of the caption of this article, in cases where the marketing authorization request refers to more than one concentration, the production dossier must be submitted for the highest and lowest concentration, provided that the formulations are qualitatively equal, proportional, and manufactured in the same place and with the same production process.

Paragraph 6. In compliance with subitem "c" of item IV of the caption of this article, justification of the specifications and analytical methods with the respective validations for non-pharmacopoeial API must be submitted.

Paragraph 7. In compliance with item V of the caption of this article, in addition to the previous provisions, companies intending to import medicinal products shall have to submit methodology and analytical reports of physicochemical, chemical, microbiological, and biological quality control and their respective validations, carried out by the importer, according to the pharmaceutical form of the finished product, bulk product, or product in the primary packaging.

Paragraph 8. In compliance with item VIII of the caption of this article, the respective marketing authorization number for diluent/ reconstituting solution accompanying the medicinal product to be authorized must be submitted.

Paragraph 9. In compliance with item VIII of the caption of this article, if the diluent/ reconstituting solution has not been authorized by Anvisa, the company must submit documentation according to the specific legislation in force.

Paragraph 10. In compliance with item VIII of the caption of this article, the accessory must mandatorily be in adequate quantity and graduation considering its dosage, where applicable.

Paragraph 11. Regarding the shelf life provided for in subitem "a" of item IX of the caption of this article, in the case of imported bulk product, the period must be counted from the date of manufacture abroad and not from the date of packaging in Brazil, observing the shelf life authorized by Anvisa.

Article 18. The batch size to be authorized refers to the batch used for the proof of safety and efficacy demonstrated through pharmaceutical equivalence, bioequivalence, and clinical studies, accordingly.

Paragraph 1. The batch size to be considered for the approval of the marketing authorization of generic and similar medicinal products must have as a reference the batch size used for the proof of pharmaceutical equivalence and bioequivalence.

Paragraph 2. The approval of a range for industrial batch size is allowed, provided that all required documentation and evidence are submitted according to the specific legislation in force for post-marketing authorization alterations.

Paragraph 3. The batch size to be considered for the approval of the marketing authorization of a new drug product must be the one referring to the batch size used for the proof of safety and efficacy.

Paragraph 4. Anvisa may consider, for marketing authorization approval, a batch size different from the one described in the caption of this article, provided that the company presents the history of alterations in formulations, production processes, batch sizes, and manufacturing sites occurred during clinical development and the results of comparability studies carried out with the medicinal product to be granted marketing authorization.

Article 19. If the company requests concomitantly to the marketing authorization the inclusion of more than one manufacturing site of the medicinal product or more than one manufacturing site of the active pharmaceutical ingredient (API), it must submit all the

additional documentation and evidence required in the specific legislation in force for post-marketing authorization alterations.

Sole paragraph. For cases where the specific legislation in force for post-marketing authorization alterations requests the submission of a stability study protocol, the complete accelerated study and the long-term study in progress must be submitted for marketing authorization.

Section IV

Technical Documentation of Safety and Efficacy for New and Innovative Medicinal Products

Article 20. To prove safety and efficacy for the marketing authorization of new and innovative medicinal products, the following must be presented:

I – non-clinical and clinical evidence including at least:

- a) non-clinical pharmacological and toxicological characterization; and
- b) biopharmaceutical, pharmacological, safety and efficacy clinical characterization.

II – clinical rationale of medicinal product development, presenting the scientific background of the development program conducted and a discussion of the innovations of the medicinal product proposed for marketing authorization in relation to the therapeutic options already authorized;

III – contextualization of the clinical condition for which the product is intended, including the therapeutic options available in Brazil, discussion of clinical practice and national epidemiological data, when available;

IV – benefit-risk assessment, with an integrated critical analysis for the proposed medicinal product under the intended conditions of use, considering the safety and efficacy data submitted; and

V – Risk Management Plan, prepared in accordance with Collegiate Board Resolution – RDC no. 406 of 22 July 2020, and its updates.

Sole paragraph. The documentation described in item I of the caption of this article must be elaborated with data obtained through full development or through abbreviated development, according to specific guides.

Article 21. For the marketing authorization of a medicinal product containing the combination of two or more APIs, in addition to the provisions of Article 20, the following must also be submitted:

I – evidence of the clinical relevance of the function of each of the APIs in the clinical indication claimed for the combination;

II – information on the pharmacokinetic and pharmacodynamic interactions between the APIs that make up the combination; and

III – technical justification with the clinical and pharmacological rationale for the association, demonstrating the following:

- a) increase in the safety or efficacy of the API(s) in the combination, due to additive or synergistic pharmacological activity or through reduction in resistance;
- b) minimization of the potential for abuse;
- c) improved bioavailability of the main API; or
- d) simplification of the therapeutic regimen.

Paragraph 1. Marketing authorization of a medicinal product containing a combination of two or more APIs in association in fixed doses or in kits may be accepted.

Paragraph 2. The marketing authorization of an association in the form of a kit shall be allowed only when there is a clear therapeutic benefit of the association and the impossibility of granting marketing authorization for an association in fixed doses in any pharmaceutical form is pharmacotechnically justified.

Article 22. The documentation of the medicinal product's safety and efficacy must include all available clinical information, both favorable and unfavorable for the medicinal product proposed for marketing authorization, and the bibliographical references used.

Article 23. If the medicinal product proposed for marketing authorization is commercialized in other countries, an updated periodical report on the benefit-risk assessment of the medicinal product must be submitted together with the marketing authorization application.

Article 24. The documents submitted for proof of safety and efficacy must be prepared in accordance with Brazilian guides or, in their absence, international guides from regulatory authorities with technical requirements similar to those adopted by Anvisa.

Subsection I

Full Development Pathway

Article 25. The full development pathway applies to the request for marketing authorization for a new or innovative medicinal product where the information required to confirm the safety and efficacy of the medicinal product proposed for marketing authorization is obtained from studies conducted by or for the applicant and for which full reports must be submitted.

Paragraph 1. The marketing authorization applicant must have access to the raw data from the studies submitted.

Paragraph 2. Anvisa may, at its discretion, request raw data from the company or conduct inspections to verify compliance with Good Clinical Practices in the conduction of studies presented to support the marketing authorization for the medicinal product.

Article 26. The marketing authorization for a new medicinal product must be submitted through the full development pathway, and the abbreviated development pathway may be accepted in the following situations:

- I – medicinal product for serious debilitating condition, and such medical need has been confirmed as unmet;
- II – medicinal product used in public health emergencies;

III – medicinal product for rare, neglected, emerging or re-emerging diseases;

IV – prescription medicinal product that has been granted marketing authorization and commercialized for more than 10 years in regulatory authorities with technical requirements similar to those adopted by Anvisa;

V – medicinal product with an API analogous to the API of a product already granted marketing authorization, in cases where the applicant for marketing authorization confirms that there are no significant differences in the safety and efficacy profile between the medicinal product being proposed for marketing authorization and the medicinal product already granted marketing authorization, which would preclude the use of existing data or, in the case of any differences, that these are duly justified and scientifically substantiated so as to enable the use of existing data; or

VI – medicinal product with API of another product previously granted marketing authorization in Brazil, but with a marketing authorization no longer valid.

Paragraph 1. For acceptance of the abbreviated development pathway in the terms of the caption of this article, proof of current commercialization experience is required, demonstrating the established use of the API abroad under similar conditions of use, with recognized efficacy and acceptable level of safety.

Paragraph 2. If the invalidation of the marketing authorization under the terms of item VI of this article results from safety and efficacy deficiencies, these must be technically corrected.

Subsection II

Abbreviated Development Path

Article 27. The abbreviated development pathway applies to the request for marketing authorization for a new or innovative medicinal product where part of the information required to confirm safety and efficacy of the medicinal product is obtained from studies not conducted by or for the applicant.

Paragraph 1. For marketing authorization submissions through abbreviated development, scientific rationale must be presented to justify the option for this route in lieu of the full development.

Paragraph 2. In cases where studies submitted to confirm safety and efficacy have been conducted by or at the request of the marketing authorization applicant, the complete study reports must be submitted, and the applicant must have access to the raw data of the studies presented.

Paragraph 3. For the cases provided for in Paragraph 2 of this article, Anvisa may, at its discretion, request the company to provide the raw data of the studies presented or conduct inspections to verify compliance with Good Clinical Practices in the conduction of the studies presented to support the marketing authorization of the medicinal product.

Article 28. For marketing authorization applications through the abbreviated development pathway, the following may be accepted as evidence of safety and efficacy:

I – clinical studies;

II – non-clinical studies;

III – bridging studies;

IV – scientific literature; or

V – technical data.

Paragraph 1. In cases where the evidence presented to corroborate safety and efficacy is not obtained from studies conducted with the medicinal product proposed for marketing authorization, the company must present bridging studies that allow the extrapolation of such evidence to the medicinal product being proposed for marketing authorization.

Paragraph 2. In cases where the main safety and efficacy evidence is based on data from scientific literature or technical data, the marketing authorization application must be accompanied by bridging studies between the medicinal product proposed for marketing authorization and a comparator medicinal product, in addition to proof of current commercialization experience, demonstrating the established use of the API abroad under similar conditions of use, with recognized efficacy and acceptable level of safety.

Paragraph 3. The acceptability of submissions based on scientific literature and technical data shall be assessed according to the characteristics of each submission, considering the need to conduct confirmatory clinical trials, the therapeutic class, and the health risk of the medicinal product proposed for marketing authorization.

Paragraph 4. The comparator medicinal product to be used in the bridging studies must have efficacy, safety, and quality scientifically proven to the competent health authority, and it may be the Brazilian reference medicinal product or another one agreed upon with Anvisa.

Article 29. The relative bioavailability studies and biowaiver tests presented as main safety and efficacy evidence or as bridging studies that support the marketing authorization for a new or innovative medicinal product must meet the requirements provided for in Collegiate Board Resolution – RDC no. 742 of 10 August 2022 and Collegiate Board Resolution – RDC no. 749 of 5 September 2022, and their updates.

Paragraph 1. In cases where relative bioavailability studies are conducted to demonstrate intentional differences in pharmacokinetic parameters between the proposed medicinal product and the comparator medicinal product, the company must present the scientific rationale and complementary data confirm safety and efficacy of the medicinal product proposed for marketing authorization.

Paragraph 2. The pharmacokinetic interaction studies that support the marketing authorization for associations, as provided for in item II of Article 21, must meet the requirements set forth in the specific legislation in force.

CHAPTER IV

SPECIFIC REQUIREMENTS FOR THE MARKETING AUTHORIZATION FOR GENERIC AND SIMILAR MEDICINAL PRODUCTS

Article 30. The following shall not be admitted for the purposes of marketing authorization as generic or similar medicinal products:

- I – biological, immunotherapeutic, plasma-derived, and blood-derived products of human origin;
- II – herbal medicinal products;
- III – specific medicinal products;
- IV – dynamized medicinal products;
- V – medicinal products of simplified notification;
- VI – antiseptics for hospital use;
- VII – products for diagnostic purposes and radiological contrasts;
- VIII – radiopharmaceuticals;
- IX – medicinal gases; and
- X – other classes of medicinal products that may have specific legislation for their marketing authorization.

Section I

Pharmaceutical Equivalence Studies and Dissolution Profile

Article 31. The application for the marketing authorization for similar and generic medicinal products, in addition to the documentation referred to in Sections II and III of Chapter III, must be accompanied by a certificate of pharmaceutical equivalence, a dissolution profile certificate, and a dissolution method development report, in accordance with the specific legislation in force.

Sole paragraph. The provisions in the caption of this article do not apply if the manufacture of the generic or similar medicinal product and of the reference medicinal product is carried out at the same manufacturing site, with identical formulation, production process, and equipment.

Section II

Bioequivalence Studies

Article 32. For the marketing authorization application for similar and generic medicinal products, in addition to the documentation referred to in Sections II and III of Chapter III, bioequivalence studies or biowaiver tests must be submitted in accordance with the guidelines available on Anvisa's website.

Article 33. The bioequivalence study or biowaiver tests must be carried out, mandatorily, with the same batch used in the pharmaceutical equivalence study.

Sole paragraph. If it is impossible to use the same batch, a plausible justification must be presented for conducting the studies with different batches, in accordance with the specific legislation in force.

CHAPTER V

FINAL AND TRANSITIONAL PROVISIONS

Article 34. Anvisa may, at its discretion and upon technical justification, require additional evidence or new studies to confirm the efficacy, safety, and quality of the medicinal product proposed for marketing authorization.

Sole paragraph. The requirement for additional evidence or new studies may occur even after the marketing authorization has been granted.

Article 35. Applications for marketing authorization for a medicinal product in the category of new or innovative medicinal product shall not be accepted for medicinal products likely to be classified as generic or similar medicinal products.

Paragraph 1. The provisions in the caption of this article do not apply to cases where the medicinal product already granted marketing authorization has been submitted through the abbreviated development pathway and the proposed medicinal product has generated the safety and efficacy evidence referenced in the development of the medicinal product already granted marketing authorization.

Paragraph 2. The marketing authorization may be granted for the category of innovative medicinal products in the cases where the application for marketing authorization as a new or innovative medicinal product with the same APIs, same pharmaceutical form, same concentration, and same therapeutic indications is submitted before the publication of the marketing authorization for another medicinal product with the same characteristics, and where the evidence of safety, efficacy, and quality is presented according to this technical requirement.

Paragraph 3. In the cases where the development of the medicinal product has been conducted through the development of a new or innovative medicinal product, in the terms of Section IV of Chapter III of this Resolution, but the application for marketing authorization is submitted after the publication of the marketing authorization for another medicinal product with the same APIs, same pharmaceutical form, same concentration, and same therapeutic indications, considering that the evidence of safety, efficacy, and quality is presented according to this technical requirement, the marketing authorization may be granted in the category of similar medicinal product, provided that evidence of equivalence to the reference medicinal product is presented in up to 24 months.

Article 36. The company that holds the marketing authorization or manufactures the medicinal product may be inspected for on-site verification of data and information presented in the application for marketing authorization, at Anvisa's discretion.

Article 37. Anvisa shall establish the innovation level of innovative medicinal products in a specific normative instrument.

Article 38. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, pursuant to Law no. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 39. Applications for the granting of marketing authorization for new, innovative, generic, and similar medicinal products submitted before the date this Resolution enters into force, or which are already under analysis at Anvisa, shall be analyzed in accordance with the Resolutions in force at the time of submission.

Sole paragraph. The applications that meet the requirements of this Resolution and were submitted prior to its effectiveness may be assessed in the terms of this Resolution.

Article 40. For the medicinal products under development on the date this Resolution enters into force, the development previously agreed shall be accepted, according to the period defined in the agreement formalization instrument.

Article 41. Collegiate Board Resolution – RDC no. 200 of 26 December 2017, published in the Federal Official Gazette no. 248 of 28 December 2017, Section 1, page 84, is hereby revoked.

Article 42. This Resolution enters into force on 1 November 2022.

ANTONIO BARRA TORRES

Director-President

ANNEX I

PRODUCTION REPORT

Header	
Active Ingredient (DCB)	
Trade name	
Differential complement	
Pharmaceutical Form	
Concentration	
Therapeutic Class and ATC code	
Name and address of the API manufacturing company	

Master Formula					
Substance	DCB Number	Quantity	% of pharmaceutical form	Function in the Formula	Quality control of specification references

Batch information			
Size of pilot batch/ biobatch			
Size of industrial batch ¹			
Numbers of pilot or industrial batches manufactured ¹	Batch 1 (Biobatch)	Batch 2	Batch 3
Batch number of the API used in batch production			

Production dossier ²	
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Production process	
Name and full address (including city, country, and CNPJ) ³	
List of equipment (including identification per type, automation, working capacity, design, and principle of operation)	
Description of the pharmacotechnical process ⁴	
In-process control methodologies (including bibliographic reference – Validation)	

Production flowchart					
Stage ⁵	Substance ⁶	Unit Operation	Parameters of the unit operation ⁷	Equipment	In-process control ⁸

1. Industrial batch size to be approved at marketing authorization, according to the Paragraphs of Article 18.

2. Send a copy of the production dossier for the batch/ biobatch. For the other two batches, send only the copies of the quality control analysis reports for the medicinal product.

3. Name and responsibility of each manufacturer, including subcontracted companies and each proposed manufacturing site involved in production, including quality control.
4. Describe the process in the form of topics, numbering each one of the stages.
5. According to the numbering in the description of the pharmacotechnical process.
6. Indicate the order of addition of the substances at the stage where it occurs.
7. Information regarding speed, temperature, time, etc. The associated numerical values may be presented as expected ranges. Numerical ranges for critical stages must be justified. In certain cases, environmental conditions (e.g., low humidity for effervescent products) must be listed.
8. Inform which tests will be carried out and at what stage they will occur.