COLLEGIATE BOARD RESOLUTION – RDC NO. 200 of 26 DECEMBER 2017

Provides for the criteria for the granting and renewal of the marketing authorization of medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products, and gives other provisions.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and item V, paragraphs 1 and 3 of Article 53 of the Internal Regulation approved in the terms of Annex I of Collegiate Board Resolution – RDC no. 61 of 3 February 2016, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 12 December 2017, and I, Director-President, determine its publication:

Article 1. The Technical Regulation that establishes the minimum requirements for the granting and renewal of the marketing authorization of medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products is approved, in the terms of this Resolution.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 2. This Resolution has the objective of establishing the criteria and minimum documentation required for the granting and renewal of the marketing authorization of medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products, aiming at ensuring the quality, safety, and efficacy of such medicinal products.

Section II

Scope

Article 3. This Regulation applies to all medicinal products with synthetic and semisynthetic active ingredients, classified as new, generic, and similar medicinal products, except those ruled by specific legislation in force.

Section III

Definitions

Article 4. 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 (Resolution – RDC no. 31 of 11 August 2010);

II – bioavailability: indicates absorption speed and extent 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;

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

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

V – biobatch: batch used for the proof of pharmaceutical equivalence and bioequivalence;

V-A – Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA): administrative instrument that attests the adequacy of the Active Pharmaceutical Ingredient Dossier (DIFA); **(Included by Resolution – RDC no. 361 of 27 March 2020)**

VI – Good Manufacturing Practices Certificate (GMPC): document issued by Anvisa certifying that a given establishment complies with the Good Manufacturing Practices as provided for in the health legislation in force (Resolution – RDC no. 39 of 14 August 2013);

VII – 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 (OMS, 2013);

VIII – 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;

IX – Brazilian Common Denomination (DCB): generic nomenclature attributed to the pharmaceutical inputs, according to the relationship established by the Brazilian Pharmacopoeia;

IX-A – Active Pharmaceutical Ingredient Dossier (DIFA): set of administrative and technical documents of an active pharmaceutical ingredient; **(Included by Resolution – RDC no. 361 of 27 March 2020)**

X – package: wrap, recipient, or any form of packaging, removable or not, destined to cover, package, fill, protect, or keep, specifically or not, medicinal products (Law no. 6,360 of 23 September 1976, and Resolution – RDC no. 71 of 22 December 2009);

XI – primary packaging: package that keeps direct contact with the medicinal product (Resolution – RDC no. 71 of 22 December 2009);

XII – 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 (Resolution – RDC no. 71 of 22 December 2009);

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

XIV – 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, in accordance with approval by Anvisa (Resolution – RDC no. 71 of 22 December 2009);

XV – Pharmaceutical Equivalence Study: set of physical-chemical and, when applicable, microbiologic and biologic trials, which prove that two medicinal products are pharmaceutical equivalents (Resolution – RDC no. 31 of 11 August 2010);

XVI – pharmaceutical equivalents: medicinal products that have the same pharmaceutical form, the same route of administration, and the same quantity of the same active substance, i.e., the same salt or ester of the therapeutic molecule, which may or may not contain identical excipients, provided that well established for the function intended; they must comply with the same requirements of individual monograph of the Brazilian Pharmacopoeia, preferably, or with those of other official compendia, standards, or regulations approved/ endorsed by Anvisa or, in their absence, with other standards of quality and performance. Pharmaceutical forms of modified release that require container or excess may or may not contain the same quantity of active substance, provided that they release identical quantities of the same active substance in a same dose interval (Resolution – RDC no. 31 of 11 August 2010);

XVII – 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;

XVIII – radical innovation: development of a new molecule not yet authorized for commercialization in Brazil;

XIX – incremental innovation: development of improvements related to a medicinal product already authorized for commercialization in Brazil;

XX – active pharmaceutical input (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 in the diagnosis, cure, treatment, or prevention of a disease, which may also affect the structure and operation of the human body; (Resolution – RDC no. 17 of 16 April 2010 and Resolution – RDC no. 45 of 9 August 2012);

XXI – batch: defined quantity of raw material, packaging material, or product processed in one or more processes, the essential characteristic of which is homogeneity. Sometimes it may be necessary to divide a batch in 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 homogeneity (Resolution – RDC no. 17 of 16 April 2010);

XXII – pilot batch: batch of pharmaceutical product produced by a process representing and reproducing an industrial scale production batch (Normative Instruction IN no. 02 of 30 March 2009);

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

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

XXV – reference medicinal product: innovative product authorized at the federal body responsible for health surveillance and commercialized in Brazil, the efficacy, safety, and quality of which have been scientifically proven with the competent federal body, on the occasion of marketing authorization (Law no. 9,787 of 10 February 1999);

XXVI – 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. 9,787 of 10 February 1999);

XXVII – 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 authorized at the federal body responsible for the health surveillance, which may differ only in characteristics related to size and shape of the products, expiration date, package, labeling, excipients, and vehicles, and must always be identified by commercial name or brand; (Provisional Measure no. 2,190- 34 of 2001);

XXVIII – new medicinal product: medicinal product with new Active Pharmaceutical Ingredient API in Brazil;

XXIX – innovative medicinal product: medicinal product with incremental innovation, with development of improvements related to a medicinal product already authorized in Brazil, including new salts, isomers or mix of isomers, esters or ethers of molecules already authorized;

XXX – name of medicinal product: designation of the pharmaceutical product technically developed, in order to distinguish it from others, even if it has the same marketing authorization holder;

XXXI – batch number: printed designation 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, localize and review all manufacturing and inspection operations carried out during production (Law no. 6,360 of 23 September 1976);

XXXII – bulk product: any product that has passed through all production stages, without including the packaging process. Sterile products in their primary package are considered as bulk products (Resolution – RDC no. 17 of 16 April 2010);

XXXIII – finished product: a product that has passed through all production stages, including labeling and final packaging (Resolution – RDC no. 17 of 16 April 2010);

XXXIV – intermediate product: partially processed product containing the API and that must be submitted to subsequent manufacturing stages before becoming a bulk product (Adapted from Resolution – RDC no. 17 of 16 April 2010).

CHAPTER II

GENERAL PROVISIONS

Article 5. All documents must be sent as printed copy, numbered and initialed on all pages.

Paragraph 1. The documentation must be presented in accordance with the order provided for in this Resolution, accompanied of an index with the numbering of the respective pages of the documents.

Paragraph 2. The marketing authorization petitioner must attach to hard paper documentation an electronic media containing the file in searchable and reproducible PDF format, with all requirements provided for in the caption of this article.

Paragraph 3. The provisions in the caption of this article do not apply to the cases of submission through electronic means.

Article 6. The official documents in foreign language used for the purposes of marketing authorization, issued by health authorities, must be accompanied of sworn translation in the form of the law.

Article 7. For the purposes of the provisions in this Regulation, if there is specific legislation or guides, these must be complied with and the respective evidences must be presented.

Sole paragraph. Anvisa may require, at its discretion and upon technical justification, tests and documents that must be submitted in cases not provided for in this Resolution, or that do not comply with any of the requirements specified.

Article 8. The size of the batch to be authorized shall refer to the batch used for the proof of safety and efficacy demonstrated by means of pharmaceutical equivalence, bioequivalence, and clinical trials, accordingly.

Paragraph 1. The size of batch to be considered for approval of the marketing authorization of generic and similar medicinal products must have as a reference the size of the batch used for proof of pharmaceutical equivalence and bioequivalence. The approval of a range for industrial batch size will be allowed, provided that all documentation and evidences required are presented in accordance with the specific legislation in force on post-marketing authorization alterations.

Paragraph 2. The size of batch to be considered for approval of the marketing authorization of a new medicinal product must be the one referring to the size of the batch used for proof of safety and efficacy. Anvisa may consider, for approval of the marketing authorization, a batch

size different from that 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 made during the clinical development and the results of comparability studies carried out with the medicinal product intended for marketing authorization.

Article 9. In case the company requests, concomitantly to the marketing authorization, the inclusion of another manufacturing site for the medicinal product or another manufacturing site for the active pharmaceutical input (API), it must present the whole documentation and additional evidences required in the specific legislation in force for post-marketing authorization alterations.

Sole paragraph. For the cases where the specific legislation in force for post-marketing authorization alterations requires the presentation of the stability studies protocol, the complete accelerated study and the long-term study in course must be presented for marketing authorization.

Article 10. New medicinal products and similar medicinal products must adopt obligatorily the name of the medicinal product, in accordance with the specific legislation in force.

Article 11. The presentations of the medicinal product intended for marketing authorization must be in accordance with the medicinal product posology and therapeutic indication.

Article 12. Anvisa may, at its discretion and upon technical justification, require additional evidences of quality of medicinal products and require new studies for quality, safety, and efficacy.

Paragraph 1. Anvisa may request the company the raw data of clinical and non-clinical trials, as well as the quality data of the medicinal product.

Paragraph 2. The requirement of additional evidence may occur even after the marketing authorization is granted.

Article 13. In the cases provided for in the regulation requesting the presentation of a Pharmacovigilance Plan or Report, or Risk Minimization Plan, or the Executive Summary referring to the period of five years of the Pharmacovigilance Periodic Report, the documentation must be submitted by means of a document directed to the area of Anvisa responsible for the pharmacovigilance of medicinal products, after the petitioning of the marketing authorization or renewal.

Article 14. The report of clinical trials, when requested, must include, in addition to the provisions in the specific requirements, the following information:

I – bibliographic references, as available;

II – all the clinical information available, favorable, and unfavorable to the medicinal product at trial.

Article 14-A. The marketing authorization petitioner is responsible for the quality of the API used in the medicinal product manufacture. **(Included by Resolution – RDC no. 361 of 27 March 2020)**

CHAPTER III

GENERAL REQUIREMENTS FOR MARKETING AUTHORIZATION

Section I

Measures Prior to the Marketing Authorization for a New Medicinal Product

Article 15. All clinical trials conducted in Brazilian territory for the purposes of marketing authorization must comply with the specific legislation in force for clinical research.

Sole paragraph. The previous approval of the clinical development conducted in Brazilian territory is mandatory for the use of results for marketing authorization purposes.

Article 16. The marketing authorization petitioner must request to the Brazilian Pharmacopoeia the inclusion of the API and excipient in the Brazilian Common Denomination (DCB), in case the latter is not yet present in such list.

Section II

Measures Prior to the Marketing Authorization for an Innovative Medicinal Product

Article 17. All clinical trials conducted in Brazilian territory for the purposes of marketing authorization must comply with the specific legislation in force for clinical research.

Sole paragraph. The previous approval of the clinical development conducted in Brazilian territory is mandatory for the use of results for marketing authorization purposes.

Article 18. All marketing authorization requests to be petitioned through the categories described in Sections VII and VIII of CHAPTER V must submit the Protocol containing the Clinical Rationale for Evidence of Safety and Efficacy for previous assessment by Anvisa.

Section III

Measures Prior to the Marketing Authorization for Generic and Similar Medicinal Products

Article 19. The marketing authorization petitioner must check the list of reference medicinal products available at Anvisa website, to verify if there is a reference medicinal product elected in the concentration and pharmaceutical form for the medicinal product intended for marketing authorization.

Sole paragraph. In the absence of the reference medicinal product elected, the request for election of reference medicinal product must be filed with Anvisa, in accordance with the specific legislation in force.

Article 20. The following shall not be accepted for marketing authorization purposes as generic or similar medicinal products:

I – biologicals, immunotherapy products, derived from human plasma and blood;

II – herbal medicinal products;

III – specific medicinal products;

IV – dynamized medicinal products;

V – simplified notification medicinal products;

VI –antiseptic agents for hospital use;

VII – products with radiological contrasts and diagnostic purposes;

VIII – radiopharmaceuticals;

IX – medicinal gases; and

X – other classes of medicinal products that may have specific legislation for marketing authorization.

Section IV

Administrative Documentation

Article 21. The medicinal product marketing authorization petition pursuant to this Resolution must be individualized for each pharmaceutical form.

Sole paragraph. For generic and similar medicinal products in which different concentrations for the same pharmaceutical form have different reference medicinal products elected, the process must be the same.

Article 22. All petitions filed must be accompanied by the following documents:

I – petition 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, accordingly;

III – model of the package insert text;

IV – layout of primary and secondary packages of each presentation of the medicinal product, referring to each manufacturing site;

V – copy of valid Good Manufacturing Practices Certificate – GMPC issued by Anvisa, for the production line in which the medicinal product, object of registration, will be manufactured, or yet, copy of the inspection request protocol for the purposes of issuance of the GMPC; and

Paragraph 1. In case there is more than one manufacturing site or location of production stages, the documentation described in item V must be presented for each company involved in the production chain of the medicinal product.

Paragraph 2. For cases where Anvisa and the competent regulatory authority of the country manufacturing the concerned medicinal product conclude for the equivalence of measurements and controls applied to confirm the good manufacturing practices, a document confirming the good manufacturing practices issued by the Health Surveillance authority in the manufacturing country may be submitted.

Paragraph 3. For intermediate products, a document confirming the good manufacturing practices issued by the Health Surveillance authority in the manufacturing country may be submitted.

Paragraph 4. In the case of imported products, the copy of the inspection request protocol for the purposes of issuance of the GMPC must be accompanied of a copy of the document confirming the good manufacturing practices for pharmaceutical products per valid production line, issued by the Health Surveillance authority in the manufacturing country.

Paragraph 5. The lack of the valid GMPC shall not hinder the submission of the marketing authorization petition, but shall hinder its approval.

Article 23. In addition to the list of documents contained in Article 22, for imported medicinal products, the phase of the medicinal product to be imported as finished product, bulk product, or product in primary package must be informed.

Sole paragraph. For a new medicinal product, information must be submitted, when available, on any commitments with other agencies related to the conduction of complementary clinical safety, clinical efficacy, clinical pharmacology, or non-clinical toxicology studies. Failure to submit such information shall not hinder the submission of the marketing authorization petition.

Section V

Quality Technical Documentation

Subsection I

Active Pharmaceutical Ingredient

(Included by Resolution – RDC no. 361 of 27 March 2020)

Article 23-A. When submitting the petition for medicinal product marketing authorization, the petitioner must present the following information regarding the API:

(Included by Resolution – RDC no. 361 of 27 March 2020)

I – letter from the DIFA holder, on behalf of the medicinal product marketing authorization petitioner 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 petition; **(Included by Resolution – RDC no. 361 of 27 March 2020)**

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. The statement must be based on an audit of good manufacturing practices conducted in accordance with the Collegiate Board Resolution – RDC, which provides for the general guidelines for the good manufacturing practices for medicinal products; **(Included by Resolution – RDC no. 361 of 27 March 2020)**

III – expedient number of the API GMP certificate petition, in accordance with the Collegiate Board Resolution – RDC that provides for the certification of good manufacturing practices for APIs; **(Included by Resolution – RDC no. 361 of 27 March 2020)**

IV – when there is a confidentiality restriction of the DIFA, statement of the technical responsible person of the marketing authorization petitioner, or person designated by him/ her, that the

marketing authorization petitioner has possession of the open part; **(Included by Resolution – RDC no. 361 of 27 March 2020)**

V – for sterile API, description and validation of the API sterilization process, when not carried out under the responsibility of the DIFA holder; and **(Included by Resolution – RDC no. 361 of 27 March 2020)**

VI – description of the physical steps (micronization, grinding, sieving, lyophilization), when not carried out under the responsibility of the DIFA holder. **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1. It is the marketing authorization petitioner's responsibility to assess the suitability of the API specification to the maximum daily dose, route of administration, and pharmaceutical form of the medicinal product subject to marketing authorization. **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 2. Granting of the medicinal product marketing authorization will be conditioned to valid API GMP certificate and CADIFA. **(Included by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 3. If the DIFA holder already has a CADIFA, the marketing authorization petitioner 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 petitioner.

Paragraph 4. For API that does not fall within the scope of the Collegiate Board Resolution – RDC establishing the DIFA and the CADIFA, the documentation required in specific regulation must be submitted, as applicable, replacing the documents requested in the caption of this article. **(Included by Resolution – RDC no. 361 of 27 March 2020)**

~~Article 24. When submitting a medicinal product marketing authorization petition, the marketing authorization petitioner must present a technical report containing the following information:~~

~~I – about the active pharmaceutical input (API):~~

~~a) nomenclature: Brazilian Common Denomination (DCB);~~

~~b) structure: structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass;~~

~~c) physicochemical properties: physical form, stoichiometric ratio between the chemical form of the API presentation and its pharmacodynamically active component, melting point, solubility, particle size, and pKa;~~

~~d) name of the manufacturer(s) of the API(s) with the respective address(es) and document of the official health authority of the country of origin confirming the authorization for the activity of manufacturing API;~~

~~e) description of the synthesis process: flowchart of the synthesis process, including molecular formula, chemical structures of starting materials, intermediates and their nomenclatures, solvents, catalysts, reagents, and the API, contemplating stereochemistry;~~

~~f) elucidation of the structure and other characteristics and impurities: confirmation of structure based on the synthesis route and spectral analysis, covering the infrared spectrum of the~~

~~molecule and other analyses necessary for the correct identification and quantification of the molecule(s), and information on potential structural and geometric isomerism, specific optical rotation, refractive index, chirality, potential to form polymorphs, detailing its characteristics and of other polymorphs related to the API, and information on impurities;~~

~~g) quality control: specifications, justification of specifications for not pharmacopoeial API, analytical methods used, and validation and analysis report of a batch issued by the API manufacturer; and~~

~~h) stability: a summary of the types of studies conducted and the results, in accordance with specific legislation in force, including the results of forced degradation and stress conditions studies and their respective analytical procedures, as well as conclusions on expiration or retest date and packaging material.~~

~~II – about formulation development:~~

~~a) summary on the formulation development, taking into account the route of administration and use, as well as the packaging system;~~

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

~~c) documents with details of manufacturing, 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 assessment of the efficacy of the preservative system used in the formulation; and~~

~~e) justification in the case of excess active ingredient.~~

~~III – about the finished product:~~

~~a) detailed description of the complete formula, designating the components according to the Brazilian Common Name (DCB, in Portuguese);~~

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

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

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

~~IV – about 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 steps of the manufacturing process showing where materials enter the process, identifying the critical points of the process and control points, intermediary tests, and control of the final product;

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

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

f) control of critical steps 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 steps with the respective justifications, parameters assessed, and indication of the results obtained and conclusion.

V – about the quality control of raw materials:

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

b) additional information for excipients of animal origin in accordance with 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.

VI – about the finished product quality control:

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

b) dissolution profile chart, where applicable.

VII – about the primary packaging and functional secondary packaging:

a) description of the packaging material; and

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

VIII – about the intermediate wrap: description of the constitution material of the intermediate wrap and its specifications;

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

X – about the stability studies of the finished product:

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

b) results of stability studies for medicinal products that, after open 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. The information in item I and its subitems must confirm authenticity of origin of the API(s), and the manufacturer(s) of such are entitled to send to Anvisa, within 30 (thirty) days after the marketing authorization submission, the documentation referred to, duly identified with the process number it relates to.~~

~~Paragraph 2. In compliance with item I, the number of marketing authorization process and the marketing authorization number of the API must be submitted for API authorized by Anvisa, replacing the documents referred to in subitems b, e, f, and h.~~

~~Paragraph 3. In compliance with subitem g of item I, justifications for the specifications for non-pharmacopoeial API must be submitted.~~

~~Paragraph 4. In compliance with subitem b of item II, in case of associations, a discussion must be presented on the compatibility among the active ingredients and among these and the excipients.~~

~~Paragraph 5. In compliance with item II, for generic and similar medicinal products, the development report of the dissolution method must be submitted, in accordance with the specific legislation in force.~~

~~Paragraph 6. In compliance with subitem a) of item III, in the absence of the DCB for an excipient used in the formulation, submit the confirmation of the request for inclusion in DCB list or a justification for the absence issued by the Brazilian Pharmacopeia.~~

~~Paragraph 7. The information in items III and IV and its subitems must be presented in accordance with the provisions in Annex I.~~

~~Paragraph 8. In compliance with subitem a) of item IV, in the cases where the marketing authorization petition refers to more than one concentration, the production dossier must be presented for the highest and the lowest concentration, provided that the formulations are qualitatively equal, proportional, and manufactured in the same site and with the same production process.~~

~~Paragraph 9. In compliance with the subitem c of item V, a justification of specifications and of analytical methods with the respective validations for non-pharmacopoeial API must be sent.~~

~~Paragraph 10. In compliance with item VI, in addition to the previous provisions, the companies intending to import medicinal products shall have to present the methodology and analytical report of physicochemical, chemical, microbiological, and biological quality control and their respective validations, carried out by the importer, in accordance with the pharmaceutical form of the finished product, bulk product, or product in the primary package.~~

~~Paragraph 11. In compliance with item IX, the respective marketing authorization number for diluent/ reconstituting solution that accompanies the medicinal product to be authorized must be submitted.~~

~~Paragraph 12. In compliance with the item IX, if the diluent/ reconstituting solution has not been authorized by Anvisa, the company must submit documentation according to the specific legislation in force.~~

~~Paragraph 13. In compliance with the item IX the accessory must mandatorily be in adequate quantity and graduation considering its dosage, where applicable.~~

~~Paragraph 14. Regarding the shelf life provided for in subitem "a" of item X, in the case of imported bulk product, the period must be counted from its manufacturing date abroad and not from the date of packaging in Brazil, observing the shelf life authorized by Anvisa.~~

Subsection II

Medicinal product

(Included by Resolution – RDC no. 361 of 27 March 2020)

Article 24. When submitting a medicinal product marketing authorization petition, the marketing authorization petitioner must submit a technical report containing the following information: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

I – about formulation development: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) summary on the formulation development, taking into account the route of administration and use, as well as the packaging system; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

b) information on the API compatibility with the excipients, the main physicochemical characteristics of the API that may influence the performance of the finished product; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

c) documents with details of manufacturing, 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; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

d) data and discussion on the assessment of the efficacy of the preservative system used in the formulation; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

e) justification in the case of excess active ingredient. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

II – about the finished product: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) detailed description of the complete formula, designating the components according to the Brazilian Common Name (DCB, in Portuguese); **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

b) information on the quantity of each component of the formula and their respective functions, including the components of the capsule, and indication of the respective references of quality specifications described in the Brazilian Pharmacopoeia or in other official codes authorized by the specific legislation in force; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

c) detailed description of the qualitative and quantitative proportion of intermediate products used in the finished product formula; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

d) justification regarding the presence of groove on the tablet with the appropriate tests. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

III – on the production of the finished product: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) production dossier related to 1 (one) batch; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

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; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

c) flowchart with the steps of the manufacturing process showing where materials enter the process, identifying the critical points of the process and control points, intermediary tests, and control of the final product; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

d) information on batch sizes of the finished product, description of the manufacturing process steps, including all parameters used, in-process control, and intermediate products; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

e) list of equipment involved in the production, identified by operating principle (class) and design (subclass) with their respective capacities; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

f) control of critical steps 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 **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

g) summary report of the manufacturing process validation, including batches, definition of the critical manufacturing steps with the respective justifications, parameters assessed, and indication of the results obtained and conclusion. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

IV – on the quality control of raw materials: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) specifications, analytical methods, and analytical reports for excipients, accompanied by bibliographic reference, made by the medicinal product manufacturer; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

b) additional information for excipients of animal origin in accordance with the specific legislation in force on the control of Transmissible Spongiform Encephalopathy; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

c) specifications, analytical methods, and analytical report for the active pharmaceutical ingredient, accompanied by bibliographic reference, carried out by the medicinal product manufacturer. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

V – about the finished product quality control: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) specifications, analytical methods, and analysis report, accompanied by bibliographic reference, including analytical method validation reports; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

b) dissolution profile chart, where applicable. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

VI – on primary packaging and functional secondary packaging: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) description of the packaging material; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

b) report with specifications, analytical method, and packaging quality control results. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

VII – on the intermediate wrap: description of the constitution material of the intermediate wrap and its specifications; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

VIII – on the accessories accompanying the medicinal product in its commercial packaging: description of the accessory composition material and its specifications; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

IX – on the stability studies of the finished product: **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

a) report with the results of accelerated and long-term stability studies conducted with 3 (three) batches, protocols used, including conclusions regarding conservation care and shelf life; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

b) results of stability studies for medicinal products that, after open or prepared, may undergo alterations in their original shelf life or original conservation care; and **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

c) results of the photostability study or technical justification for study exemption; **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 1. In compliance with subitem (b) of item I, in case of associations, a discussion must be presented on the compatibility among the active ingredients, as well as among them and the excipients. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 2. In compliance with item I, for generic and similar medicinal products, the dissolution method development report must be submitted, according to specific legislation in force. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 3. In compliance with subitem "a" of item II, 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. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 4. The information explained in items II and III and their subitems must be presented as provided in Annex I. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 5. In compliance with subitem "a" of item III, in cases where the marketing authorization request refers to more than one concentration, the production dossier must be

submitted for the highest and lowest concentrations, provided that the formulations are qualitatively equal, proportional, and manufactured in the same place and with the same production process. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 6. In compliance with subitem "c" of item IV, justification of the specifications and analytical methods with the respective validations for non-pharmacopoeial API must be submitted. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 7. In compliance with item V, in addition to the previous provisions, companies intending to import medicinal products shall have to submit methodology and analytical report 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. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 8. In compliance with item VIII, the respective marketing authorization number for diluent/ reconstituting solution that accompanies the medicinal product to be authorized must be submitted. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 9. In compliance with item VIII, if the diluent/ reconstituting solution has not been authorized by Anvisa, the company must submit documentation according to the specific legislation in force. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 10. In compliance with item VIII, the accessory must mandatorily be in adequate quantity and graduation considering its dosage, where applicable. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

Paragraph 11. Regarding the shelf life provided for in subitem “a” of item IX, in the case of imported bulk product, the period must be counted from its manufacturing date abroad and not from the date of packaging in Brazil, observing the shelf life authorized by Anvisa. **(New wording given by Resolution – RDC no. 361 of 27 March 2020)**

CHAPTER IV

SPECIFIC REQUIREMENTS FOR THE MARKETING AUTHORIZATION FOR A NEW MEDICINAL PRODUCT

Section I

Marketing Authorization for a New Medicinal Product

Article 25. This section refers to the marketing authorization of a medicinal product with a new Active Pharmaceutical Input – API;

Article 26. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – safety and efficacy report, in accordance with specific guide, containing:

a) report of non-clinical trials; and

b) report of phase I, II, and III clinical trials.

II – Pharmacovigilance plan, in accordance with the specific legislation in force.

Paragraph 1. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan provided for in item II.

Paragraph 2. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product must be presented with the marketing authorization petition.

Article 27. The company may present, exceptionally, the report of clinical trials containing completed phase II studies and initiated phase III studies, aiming at requiring the marketing authorization of a new medicinal product intended for prevention or treatment of severe life-threatening or highly debilitating diseases, provided that it is proven for both cases as an unmet medical need.

Sole paragraph. In specific cases where phase III studies are not applicable and phase II studies are sufficient to confirm the medicinal product efficacy and safety, the company may submit the marketing authorization petition after the completion of phase II studies.

CHAPTER V

SPECIFIC REQUIREMENTS FOR THE MARKETING AUTHORIZATION FOR AN INNOVATIVE MEDICINAL PRODUCT

Section I

Marketing Authorization for a New Association

Article 28. This section refers to the marketing authorization of a medicinal product composed of a new combination of two or more APIs already authorized in Brazil in:

I – a fixed ration of doses in a same pharmacotechnical unit hereinafter called association in fixed dose; or

II – a fixed ration of doses in different pharmacotechnical units in a same package, for concomitant or sequential use, hereinafter called kit.

Sole paragraph. In the cases where one or more APIs, or new salts, isomers, or a mixture of isomers, esters, ethers, complexes, or byproducts of such API(s) that compose the association is (are) not authorized in Brazil, the marketing authorization petition for this association must comply with the same requirements provided for the marketing authorization for a new medicinal product.

Article 29. The marketing authorization for new associations in the form of kit shall be allowed only when:

I – the impossibility of granting the marketing authorization for an association in fixed dose in any pharmaceutical form is pharmacotechnically justified and there is a clear benefit of the kit for public health, or

II – the impossibility of granting the marketing authorization for an association in fixed dose in any pharmaceutical form is pharmacotechnically justified, and the kit shows an increase in

adherence to the treatment, and the clinical relevance of such increase has been adequately investigated and proven for the target population.

Section II

Marketing Authorization for a New Association in Fixed Dose

Article 30. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – technical justification for the rationality of the association; and

II – safety and efficacy report, in accordance with specific guide, containing:

a) non-clinical trials, as applicable;

b) phase I and II clinical trials, as applicable, and phase III studies for each therapeutic indication, proving that:

1. associations with the same doses of the APIs have an addictive or synergic effect without increase in the risks as compared with each API separately or with combinations between them with a lower number of APIs; or

2. the association with a lower dose of, at least, one of the APIs obtains the same benefit with equal or lower risks when compared with an association with known doses.

III – Pharmacovigilance Plan adequate to the new association in fixed dose, in accordance with the specific legislation in force.

Paragraph 1. The efficacy and safety report must include information on the pharmacokinetic and pharmacodynamic interactions between the APIs that compose the association.

Paragraph 2. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan provided for in item III.

Paragraph 3. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product must be presented.

Section III

Marketing Authorization for a New Pharmaceutical Form

Article 31. This section refers to marketing authorization for a new pharmaceutical form in Brazil, for an already authorized medicinal product.

Article 32. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – technical justification;

II – safety and efficacy report in accordance with specific guide, containing the results of phase III and phase I and II clinical studies, if applicable; and

III – Pharmacovigilance Plan adequate to the new pharmaceutical form, in accordance with the specific legislation in force.

Paragraph 1. In compliance with item II, phase II and III clinical studies may be replaced with a relative bioavailability proof when the medicinal product proposed is within the approved therapeutic range.

Paragraph 2. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan.

Paragraph 3. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product must be presented together with the marketing authorization petition.

Section IV

Marketing Authorization for a New Concentration

Article 33. This section refers to the marketing authorization for a new concentration in Brazil, for an authorized medicinal product in the same pharmaceutical form.

Article 34. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – technical justification;

II – safety and efficacy report in accordance with specific guide, containing the results of phase III and phase I and II clinical studies, if applicable; and

III – Pharmacovigilance Plan adequate to the new concentration, in accordance with the specific legislation in force.

Paragraph 1. In compliance with item II, phase II and III clinical studies may be replaced with a relative bioavailability proof when the medicinal product proposed is within the approved therapeutic range.

Paragraph 2. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan.

Paragraph 3. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product must be presented together with the marketing authorization request.

Section V

Marketing Authorization for a New Route of Administration

Article 35. This section refers to the marketing authorization for a new route of administration in Brazil, for an authorized medicinal product in the same pharmaceutical form, same concentration, and same therapeutic indication.

Article 36. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – technical justification;

II – safety and efficacy report in accordance with specific guide, containing the results of phase III and phase I and II clinical studies, if applicable; and

III – Pharmacovigilance Plan adequate to the new route of administration, in accordance with the specific legislation in force.

Paragraph 1. In compliance with item II, phase II and III clinical studies may be replaced with a relative bioavailability proof when the medicinal product proposed is within the approved therapeutic range.

Paragraph 2. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan.

Paragraph 3. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product must be presented together with the marketing authorization petition.

Section VI

Marketing Authorization for a New Therapeutic Indication

Article 37. This section refers to the registration of a new therapeutic indication in Brazil, for a medicinal product already authorized in the same pharmaceutical form and same concentration.

Article 38. The marketing authorization petition described in this Section, in addition to the documentation mentioned in Section IV of Chapter III, must be accompanied of:

I – technical justification;

II – safety and efficacy report in accordance with specific guide, containing the results of phase III and phase I and II clinical studies, if applicable; and

III – Pharmacovigilance Plan adequate to the new therapeutic indication, in accordance with the specific legislation in force.

Paragraph 1. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan.

Paragraph 2. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product must be presented together with the marketing authorization petition.

Section VII

Marketing Authorization for the a Medicinal Product with the Same API(s) of a New Medicinal Product already Authorized

Article 39. This section refers to the marketing authorization for a medicinal product in case there is already a new medicinal product authorized with the same API(s).

Sole paragraph. The provisions in the caption of this article do not apply to the medicinal products classified as generic and similar medicinal products for which there is technical viability for the conduction of pharmaceutical equivalence and relative bioavailability study (bioequivalence) to confirm efficacy and safety of the medicinal product.

Article 40. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – technical justification;

II – clinical rationale for the medicinal product development;

III – Efficacy and Safety report, according to specific guide, containing:

a) scientific literature data obtained from international indexed journals with complete papers, if applicable;

b) non-clinical trial reports, if applicable; and

c) phase I, II and III clinical trial reports, if applicable.

IV – Pharmacovigilance plan, in accordance with the specific legislation in force.

Paragraph 1. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan.

Paragraph 2. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product.

Section VIII

Marketing Authorization for a Medicinal Product with a Diverse Innovation

Article 41. This section refers to the marketing authorization for a medicinal product in the case where there is an innovation in a medicinal product that is already authorized in Brazil and is not related with any marketing authorization categories previously proposed.

Article 42. The marketing authorization petition described in this section, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of:

I – technical justification;

II – clinical rationale for the medicinal product development;

III – Efficacy and Safety report, according to specific guide, containing:

a) scientific literature data obtained from international indexed journals with complete papers, if applicable;

b) non-clinical trial reports, if applicable;

c) phase I, II and III clinical trial reports, if applicable.

IV – Pharmacovigilance plan, in accordance with the specific legislation in force.

Paragraph 1. In specific situations related to safety, a Risk Minimization Plan may be required additionally to the Pharmacovigilance Plan.

Paragraph 2. In case of medicinal products commercialized in other countries, the updated Pharmacovigilance Report of the medicinal product.

Section IX

Relative Bioavailability Studies

Article 43. For the petition of a new or innovative medicinal product for which it is necessary to present the relative bioavailability studies in the terms of this Resolution, the studies must be filed according to the guides available on Anvisa website.

CHAPTER V

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

Section I

Pharmaceutical Equivalence Studies and Dissolution Profile

Article 44. The marketing authorization petition for similar and generic medicinal products, in addition to the documentation mentioned in Sections IV and V of Chapter III, must be accompanied of the pharmaceutical equivalence certificate and the dissolution profile certificate, as well as development report of the dissolution method, in accordance with the specific legislation in force.

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

Section II

Bioequivalence Studies

Article 45. The marketing authorization petition for similar and generic medicinal products, in addition to the documentation mentioned in Sections IV and V of Chapter III, the bioequivalence studies must be filed in accordance with the guides available on Anvisa website.

Article 46. The bioequivalence study or tests for bio-exemption must be performed, obligatorily, with the same batch used in the pharmaceutical equivalence study.

~~**CHAPTER VI**~~

~~**RENEWAL OF MARKETING AUTHORIZATION**~~

(Revoked by Resolution – RDC no. 317 of 22 October 2019)

~~Article 47. For the effect of renewal of marketing authorization for the medicinal product at Anvisa, all companies, in the first semester of the last year of the 5-year validity of the marketing authorization already granted, must present:~~ **(Revoked by Resolution – RDC no. 317 of 22 October 2019)**

~~I – petition forms, FP1 and FP2, duly completed and signed;~~ **(Revoked by Resolution – RDC no. 317 of 22 October 2019)**

~~II – proof of payment of the Health Surveillance Inspection Fee (TFVS, in Portuguese) and the respective Federal Collection Slip (GRU, in Portuguese), or exemption, accordingly;~~ **(Revoked by Resolution – RDC no. 317 of 22 October 2019)**

~~III – executive summary in Portuguese regarding the period of five years of the Periodic Pharmacovigilance Report of the same period; and~~ **(Revoked by Resolution – RDC no. 317 of 22 October 2019)**

~~IV – document confirming the sale in the last 5-year validity of the marketing authorization, containing the numbers of the invoices issued in Brazil and the list of buying establishments in a minimum of 1 (one) invoice issued in Brazil, per pharmaceutical form and concentration.~~ **(Revoked by Resolution – RDC no. 317 of 22 October 2019)**

~~Sole paragraph. In case of official laboratories, a non-commercialization justification must be presented when there is no production of the medicinal product in the period referred to in item IV.~~ **(Revoked by Resolution – RDC no. 317 of 22 October 2019)**

CHAPTER VII

FINAL AND TRANSITORY PROVISIONS

Article 48. The marketing authorization holding company or manufacturer of the medicinal product may be inspected for *in situ* verification of the data and information on the marketing authorization granting or renewal petition, at Anvisa's discretion.

Article 49. Information will be posted on Anvisa website with the final decision on the technical review of the medicinal product marketing authorization application.

Article 50. Anvisa may issue a technical guidance on the applicability of this Resolution for the specific cases of marketing authorization of medicinal product, such as the submission of data to confirm the safety and efficacy for the incremental innovations, as necessary.

Article 51. 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 52. Resolution – RDC no. 60 of 10 October 2014 and Resolution – RDC no. 20 of 13 May 2015 are hereby revoked.

Article 53. Marketing authorization granting petitions for new, generic, and similar medicinal products filed before the effective date of this Resolution, or that are already being reviewed by

the Medicinal Products General-Office, shall be reviewed in accordance with the Resolutions effective at the time of submission.

Article 53-A. For marketing authorization granting petitions for new, generic, and similar medicinal products filed after the effective date of this Resolution, and with batches manufactured before 12 January 2015, the following may be submitted as a replacement for the summary validation report:

I – assessment of the production process critical steps; and

II – technical justification of the absence of the other information included in the process validation summary report.

Article 54. This Resolution comes into force on the date of its publication.

JARBAS BARBOSA DA SILVA JR.

ANNEX I

PRODUCTION REPORT

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

Master Formula					
Substance	DCB Number	Quantity	% p/p of the pharmaceutical form	Function in the Formula	References of quality control specification

Batch information			
Pilot batch/ biobatch size			
Industrial batch size[1]			
Numbers of pilot or industrial batches manufactured[1]	Batch 1 (Biobatch)	Batch 2	Batch 3
Number of API batch used in batch production			

Production dossier[2]	
Production process	
Name and full address (including city, country, and the Brazilian Registry of Legal Entities – CNPJ)[3]	
List of equipment (including identification per type, automation, work capacity, design, and principle of operation)	
Description of the pharmacotechnical process[4]	
Methodologies of in-process control (including bibliographic reference – Validation)	

Production flowchart					
Stage[5]	Substance[6]	Unit Operation	Unit operation parameters[7]	Equipment	In-process control[8]

1. Size of the industrial batch to be approved in the marketing authorization, in accordance with Paragraphs of Article 8.

2. Send a copy of the production dossier referring to the batch/ biobatch. In addition, for the other two batches, send only the copies of the analysis reports of the quality control of the medicinal product, of the weighing forms, and of the yield calculation forms of the handling, packaging, and final stages.

3. Name and responsibility of each manufacturer, including subcontracted companies and each proposed manufacturing site involved in the production, including quality control.

4. Describe the process in the form of topics, numbering each of the stages.

5. In accordance with the numbering of the pharmacotechnical process description.

6. Indicate the order of addition of the substances in the stage in which this occurs.

7. Information regarding speed, temperature, time, etc. Associated numeric values may be presented as the 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 conducted and in which stage they will occur.