COLLEGIATE BOARD RESOLUTION – RDC NO. 361 OF 27 MARCH 2020

Amends Collegiate Board Resolution – RDC No. 200 of 26 December 2017 and Collegiate Board Resolution – RDC No. 73 of 7 April 2016, to provide for the submission of the Active Pharmaceutical Ingredient Dossier (DIFA) in medicinal product marketing authorization and post-marketing authorization, respectively.

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 by Collegiate Board Resolution – RDC no. 255 of 10 December 2018, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 25 March 2020, and I, Deputy Director-President, determine its publication.

Article 1. This Resolution amends Collegiate Board Resolution – RDC No. 200 of 26 December 2017 and Collegiate Board Resolution – RDC No. 73 of 7 April 2016, to provide for the submission of the Active Pharmaceutical Ingredient Dossier (DIFA, in Portuguese) in medicinal product marketing authorization and post-marketing authorization, respectively.

Article 2. Collegiate Board Resolution – RDC No. 200 of 2017 henceforth comes into force with the following alterations:

"Article 4. .....

V-A – Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA): administrative instrument that attests the adequacy of the Active Pharmaceutical Ingredient Dossier (DIFA);

.....

IX-A – Active Pharmaceutical Ingredient Dossier (DIFA): set of administrative and technical documents of an active pharmaceutical ingredient;

....." (new wording)

"Article 14-A. The marketing authorization petitioner is responsible for the quality of the API used to manufacture the medicinal product." (new wording)

"**Section V**

Quality Technical Documentation

Subsection I

Active Pharmaceutical Ingredient

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

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;

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;

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;

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;

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

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

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.

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

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." (new wording)

"**Subsection II**

Medicinal product

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

I – 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.

II – 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.

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 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.

IV – on 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.

V – 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.

VI – on primary packaging and functional secondary packaging:

a) description of the packaging material; and

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

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 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. 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.

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.

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.

Paragraph 4. The information explained in items II and III and their subitems must be presented as provided in Annex I.

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.

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.

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.

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.

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.

Paragraph 10. In compliance with item VIII, 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, 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)

Article 3. Article 12 of Collegiate Board Resolution – RDC No. 73 of 2016 henceforth comes into force with the following wording:

"Article 12.....

Paragraph 1. Alterations related to the active pharmaceutical ingredient (API) are described in Annex I, item 1 (one), alterations a; b; c; d; e; f; g; h; i; j; k; l.

Paragraph 1-A. For the replacement or inclusion of a new Active Pharmaceutical Ingredient Dossier (DIFA) without the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA), the medicinal product marketing authorization holder must file alteration "1a".

Paragraph 1-B. For API without CADIFA, the medicinal product marketing authorization holder must file all alterations related to the API provided for in the Collegiate Board Resolution – RDC that establishes the DIFA and the CADIFA, through alterations "1b", "1c", "1d", "1e", and "1f".

Paragraph 1-C. For the inclusion or replacement of CADIFA holder, the medicinal product marketing authorization holder must file alteration "1g" or "1h".

Paragraph 1-D. For API with CADIFA, when the DIFA alteration implies revision of the CADIFA, the medicinal product marketing authorization holder must file the medicinal product post-marketing authorization alteration only after approval of the DIFA alteration or expiry of the period for implementation, through alterations "1i", "1j", and "1k".

Paragraph 1-E. For API with CADIFA, when the DIFA alteration does not imply revision of the CADIFA, the medicinal product marketing authorization holder must not file a post-marketing authorization alteration of the medicinal product.

Paragraph 1-F. For API with CADIFA, the medicinal product marketing authorization holder must also file the API alterations of stages of the manufacturing process that are not included in the DIFA (e.g. sterilization, physical steps), where applicable, through alterations "1b", "1c", "1d", and "1e".

Paragraph 2. Alterations related to tests, specification limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and medicinal product are described in Annex I, item 2 (two), alterations a; b; c; d; e; f; g.

....." (new wording)

Article 4. Item 1 (one) "Alterations related to the Active Pharmaceutical Ingredient", of Annex I of Collegiate Board Resolution – RDC No. 73 of 2016, henceforth comes into force with the wording of item 1 (one) "Alterations related to the Active Pharmaceutical Ingredient" of Annex I of this Resolution.

Article 5. In Collegiate Board Resolution – RDC No. 73 of 2016, the documentation 1 of item 10 "Inclusion of new concentration" of Annex I becomes effective with the following wording:

"Documentation described in sections IV and V of Chapter III of Collegiate Board Resolution – RDC No. 200/2017, which 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, and gives other provisions. If the DIFA is the same approved for the already authorized concentration, submission of the documentation described in Subsection I of Section V of Chapter III of Collegiate Board Resolution – RDC No. 200/2017 shall be exempted." (new wording)

Article 6. In Collegiate Board Resolution – RDC No. 73 of 2016, documentation 4 of item 10 "Inclusion of new concentration" of Annex I becomes effective with the following wording:

"Documentation described in sections IV and V of Chapter III and in Chapter V (SPECIFIC REQUIREMENTS FOR MARKETING AUTHORIZATION OF GENERIC AND SIMILAR MEDICINAL PRODUCTS) of Collegiate Board Resolution – RDC No. 200/2017, which 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, and gives other provisions. If the DIFA is the same approved for the already authorized concentration, submission of the documentation described in Subsection I of Section V of Chapter III of Collegiate Board Resolution – RDC No. 200/2017 shall be exempted." (new wording)

Article 7. Alteration h "alterations made by the API manufacturer" of item 2 (two) "Alterations related to tests, specification limits, and analytical methods of the quality control and stability of the active pharmaceutical ingredient and medicinal product" of Annex I of Collegiate Board Resolution – RDC No. 73 of 2016, shall be excluded.

Article 8. The adoption of the requirements of Article 23-A, included by this Collegiate Board Resolution – RDC No. 200 of 2017, is optional for petitions of medicinal product marketing authorization and inclusion of a new concentration, pursuant to item 10 (ten) of Collegiate Board

Resolution – RDC No. 73 of 2016, the medicinal product batch of which is manufactured before 1 February 2022, provided that the petition is filed before 1 August 2023.

Sole paragraph. The transition period referred to in the caption of this article does not apply to the following APIs:

I – acyclovir;

II – sodium acyclovir;

III – ampicillin;

IV – benzathine ampicillin;

V – potassium ampicillin;

VI – sodium ampicillin;

VII – tri-hydrate ampicillin;

VIII – azithromycin;

IX – dihydrate azithromycin;

X – monohydrate azithromycin;

XI – benzylpenicillin;

XII – benzathine benzylpenicillin;

XIII – potassium benzylpenicillin;

XIV – procaine benzylpenicillin;

XV – sodium benzylpenicillin;

XVI – cabergoline;

XVII – carbamazepine;

XVIII – lithium carbonate;

XIX – carboplatin;

XX – cephalexin;

XXI – monohydrate cephalexin

XXII – sodium cephalexin;

XXIII – cephalothin;

XXIV – sodium cephalothin;

XXV – ceftazidime;

XXVI – pentahydrate ceftazidime;

XXVII – sodium ceftazidime;

XXVIII – ceftriaxone;

XXIX – ceftriaxone disodium hemi heptahydrate;

XXX – sodium ceftriaxone;

XXXI – cyclophosphamide;

XXXII – monohydrate cyclophosphamide;

XXXIII – cyclosporine;

XXXIV – ciprofloxacin;

XXXV – cisplatin;

XXXVI – clarithromycin;

XXXVII – clindamycin;

XXXVIII – cephalexin hydrochloride;

XXXIX – ciprofloxacin hydrochloride;

XL – monohydrate ciprofloxacin hydrochloride;

XLI – clindamycin hydrochloride;

XLII – monohydrate clindamycin hydrochloride;

XLIII – penicillamine hydrochloride;

XLIV – thiabendazole hydrochloride;

XLV – valaciclovir hydrochloride;

XLVI – clindamycin palmitate hydrochloride;

XLVII – clozapine;

XLVIII – efavirenz;

XLIX – phenytoin;

L – sodium phenytoin;

LI – clindamycin phosphate;

LII – thiabendazole hypophosphite;

LIII – ciprofloxacin lactate;

LIV – clarithromycin lactobionate;

LV – lamivudine;

LVI – cephalexin lysinate;

LVII – methotrexate;

LVIII – sodium methotrexate;

LIX – nevirapine;

LX – hemi-hydrated nevirapine;

LXI – penicillamine;

LXII – rifampicin;

LXIII – ritonavir;

LXIV – sultamicillin;

LXV – thiabendazole;

LXVI – sultamicillin tosylate;

LXVII – valaciclovir; and

LXVIII – zidovudine.

Article 9. For petitions for medicinal product marketing authorization and inclusion of a new concentration, pursuant to item 10 (ten) of Collegiate Board Resolution – RDC No. 73 of 2016, comprised in the transition period provided for in the caption of Article 8 and whose petitioner chooses not to adopt the requirements of Article 23-A of Collegiate Board Resolution – RDC No. 200 of 2017, the following documents on the active pharmaceutical ingredient (API) must be presented:

I – nomenclature: Common Brazilian Name (DCB);

II – structure: structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass;

III – physicochemical properties: physical form, stoichiometric relationship between the chemical form of the API presentation and its pharmacodynamically active component, melting point, solubility, particle size, and pKa;

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

V – description of the synthesis process: flowchart of the synthesis process, including molecular formula and chemical structures of starting and intermediate materials, with their respective nomenclatures, solvents, catalysts, reagents, and the API, contemplating stereochemistry;

VI – elucidation of the structure and other characteristics and impurities: confirmation of the structure based on the route of synthesis and spectral analysis, contemplating 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, refraction index, chirality, potential to form polymorphs, discriminating their characteristics and the characteristics of other polymorphs related to the API, and information on impurities;

VII – quality control: specifications, justification of specifications for non-pharmacopoeial API, analytical methods used, and validation and analysis report of a batch issued by the API manufacturer; and

VIII – stability: a summary of the types of studies conducted and the results, according to specific legislation in force, including the results of forced degradation studies and stress conditions, and

their respective analytical procedures, as well as the conclusions on the shelf life or retest period and packaging material.

Sole paragraph. The API manufacturer(s) has/ have the option to send the documentation to Anvisa, within 30 (thirty) days after submitting the marketing authorization petition, duly identified with the number of the process to which it relates.

Article 10. The adoption of the requirements described in Annex I, item 1 (one), alterations "1a", "1b", "1c", "1d", and "1e", included by this Resolution in Collegiate Board Resolution – RDC No. 73 of 2016, is optional for medicinal product post-marketing authorization petitions, whose medicinal product batch is manufactured before 1 February 2022, provided that the petition is filed before 1 August 2023.

Sole paragraph. The transition period referred to in the caption of this article does not apply to alteration "1a" of item 1 (one) of Annex I of this Resolution for the APIs of the sole paragraph of Article 8.

Article 11. For medicinal product post-marketing authorization petitions contemplated in the transition period provided for in the caption of Article 10 and whose petitioner chooses not to adopt the new requirements of Collegiate Board Resolution – RDC No. 73 of 2016, as amended by this Resolution, the documents provided for in Annex II of this Resolution, item 1 (one), alterations "1a", "1b", "1c", "1d", "1e", and "1f" must be submitted.

Article 12. This Resolution comes into force on 3 August 2020.

ANTONIO BARRA TORRES

Deputy Director-President

ANNEX I

(ITEM 1 OF ANNEX I OF COLLEGIATE BOARD RESOLUTION – RDC No. 73 of 2016)

1. ALTERATIONS RELATED TO THE ACTIVE PHARMACEUTICAL INGREDIENT

The marketing authorization holder 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 subject to post-marketing authorization.

For an API that does not fall within the scope of the Collegiate Board Resolution – RDC establishing the DIFA and the CADIFA, replacing documents 1, 2, 3 and 4, the documentation required in a specific regulation must be submitted, as applicable.

Alterations	Conditions	Documents	Type of petitioning
REPLACEMENT OR INCLUSION OF NEW DIFA WITHOUT CADIFA			
	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical		

a. inclusion or replacement of new DIFA without CADIFA	ingredient and of the medicinal product are allowed simultaneously, due to the alteration proposed. It refers to: – replacement or inclusion of a new DIFA holder without CADIFA; – inclusion of DIFA holder manufacturing process approved with substantially different synthesis route or manufacturing conditions; – inclusion of intermediate or API manufacturing site of approved DIFA holder with substantially different synthesis route or manufacturing conditions. If the petition is granted, the CADIFA will be issued and the process will be linked to the CADIFA. Petition approval is conditional on the valid API GMP certificate and CADIFA.	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.	Requires individual filing. It must await a favorable manifestation from Anvisa for implementation.

ALTERATIONS OF DIFA WITHOUT CADIFA

They refer to alterations to the previously approved DIFA without CADIFA. The following alterations require a new DIFA and, therefore, must be submitted according to the alteration "a. inclusion or replacement of new DIFA without CADIFA":

– Inclusion of manufacturing process with substantially different synthesis route or manufacturing conditions;

– Inclusion of intermediate or API manufacturing site with substantially different synthesis route or manufacturing conditions.

When the alteration of the DIFA without CADIFA refers exclusively to tests, analytical methods, and/ or acceptance criteria of the API and that, in turn, determines an alteration in tests, analytical methods, and/ or specification limits of the API by the medicinal product marketing authorization holder, the DIFA alteration may be concomitant with the alteration of item "2. Alterations Related to Testing, Specification Limits, and Analytical Methods of Quality Control and Stability of the Active Pharmaceutical Ingredient and the Medicinal Product" in Annex I of this Resolution.

For DIFA alterations not provided for in ANNEX II of the Collegiate Board Resolution – RDC establishing the DIFA, the classification must be done considering the conditions of alterations "b", "c", "d", and "e".			
b. Administrative alteration of the DIFA without CADIFA (immediate implementation)	Other administrative alterations are allowed concomitantly. 1. The alteration is exclusively administrative. 2. It refers to the following administrative alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 1.2, 1.4 and 1.5.	12	Immediate implementation. Requires individual filing.
c. Alteration of DIFA without CADIFA (HMP)	It refers to the following administrative alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 1.3, 1.6 and 1.7. It refers to the following quality alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 2.1.1, 2.1.2, 2.1.3, 2.4.1, 2.5.1, 2.5.2, 2.6.1, 2.6.2, 2.6.4, 2.6.7, 2.6.9, 2.7.1, 2.7.3, 2.7.5, 2.8.1, 2.8.2, 2.8.3, 2.9.1, 2.9.3, 2.10, 2.11.1, 2.11.2, 2.12.1, 2.12.2, 2.12.3, and 2.12.4. 1. There is no alteration in the synthesis route, including starting materials, solvents, reagents, intermediates, and purification/ isolation steps. 2. There is no impact on the impurities profile and in the API specification. The acceptance criterion restriction is an exception of the condition.	12	Immediate implementation. It does not require individual filing. HMP.

	3. For a sterile API, the alteration is not related to the sterilization step. 4. The DIFA alteration does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. 5. Regarding the API physical properties: 5.1 There is no impact on the physical properties of the API (polymorphism, particle size distribution, morphology); or 5.2 The physical properties of the API do not constitute a relevant quality attribute, considering the pharmaceutical form or manufacturing process of the medicinal product.		
d. Alteration of the DIFA without CADIFA (immediate implementation)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. It refers to the following quality alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 2.2.1, 2.2.2, 2.3.1, 2.3.2, 2.3.3, 2.3.4, 2.3.5, 2.4.2, 2.5.3, 2.6.3, 2.6.8, 2.7.2, 2.7.7, 2.7.8, 2.7.9, 2.9.2, 2.15, 2.16.2, 2.17.1, and 2.17.2. 1. There is no impact on the API impurities profile and	2, 3, 5, 6, 7, 12	Immediate implementation. Requires individual filing.

	specification. The acceptance criterion restriction and inclusion of test is an exception of the condition. 2. For sterile API, the alteration is not related to the sterilization step. 3. The alteration in API does not require an alteration in the specification of medicinal product release or stability. The medicinal product acceptance criterion restriction is an exception of the condition.		
e. Alteration of DIFA without CADIFA (major)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. It refers to the following quality alterations of the Collegiate Board Resolution – RDC establishing the DIFA: 2.1.4, 2.2.3, 2.4.3, 2.4.4, 2.4.5, 2.6.5, 2.6.6, 2.7.4, 2.7.6, 2.13.1, 2.13.2, 2.14, and 2.16.1. 1. The alteration is not classified as "1b", "1c", or "1d". Approval of the petition is conditional on valid API GMP certificate.	2, 3, 5, 6, 7, 8, 9, 10, 11, 12	Requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are		

f. Alteration of DIFA without CADIFA (major with migration to CADIFA)	allowed concomitantly, due to the alteration proposed. 1. The alteration is not classified as "1b", "1c", or "1d". 2. This alteration is alternative to alteration "1e". If the petition is granted, the CADIFA will be issued and the process will be linked to the CADIFA. Petition approval is conditional on valid API GMP certificate and CADIFA.	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
INCLUSION OR REPLACEMENT OF CADIFA HOLDER			
g. Inclusion or replacement of CADIFA holder (immediate implementation)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. There is no impact on the API impurities profile and specification. The API acceptance criterion restriction is an exception of the condition. 2. The alteration in API does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. Implementation of the alteration is conditional to valid API GMP certificate and CADIFA.	2, 3, 4, 5, 6, 7, 13	Immediate implementation. Requires individual filing.

h. Inclusion or replacement of CADIFA holder (major)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. The alteration is not classified as "1g". Approval of the petition is conditional on valid API GMP certificate and CADIFA.	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
ALTERATIONS OF THE DIFA WITH CADIFA For API manufacturing steps not included in the CADIFA (e.g. micronization or sterilization not performed under the DIFA holder's responsibility), alterations "1b", "1c", "1d", "1e", and "1f" must be used.			
i. Alteration of API with CADIFA (HMP)	1. There is no alteration in the synthesis route, including starting materials, solvents, reagents, intermediates, and purification/ isolation steps. 2. There is no impact on the API impurities profile and specification. The acceptance criterion restriction is an exception of the condition. 3. The alteration in API does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. 4. Regarding the API physical properties: 4.1 There is no impact on the API physical properties (polymorphism, particle size distribution, morphology); or	13	Immediate implementation. It does not require individual filing. HMP.

	4.2 The API physical properties do not constitute a relevant quality attribute, considering the medicinal product pharmaceutical form or manufacturing process.		
j. Alteration of API with CADIFA (immediate implementation)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. There is no impact on the API impurities profile and specification. The acceptance criterion restriction and inclusion of test is an exception of the condition. 2. The alteration in API does not require an alteration in the medicinal product release or stability specification. The medicinal product acceptance criterion restriction is an exception of the condition. Implementation of the alteration is conditional to valid API GMP certificate and CADIFA.	2, 3, 5, 6, 7, 13	Immediate implementation. Requires individual filing.
k. Alteration of API with CADIFA (major)	Alterations related to tests, specifications limits, and analytical methods of quality control and stability of the active pharmaceutical ingredient and of the medicinal product are allowed concomitantly, due to the alteration proposed. 1. The alteration is not classified as "1i" or "1j".	2, 3, 5, 6, 7, 8, 9, 10, 11, 13	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.

	Approval of the petition is conditional on valid API GMP certificate and CADIFA.		
LINKING THE CADIFA			
l. Linking the CADIFA.	1. The API manufacturer already approved in the medicinal product marketing authorization process has a valid CADIFA for the same API. 2. The conditions of the API approved in the medicinal product marketing authorization process are identical to those of the API for which CADIFA was granted (manufacturer of API and intermediaries, starting material, synthesis route, manufacturing process, specifications of the API and its intermediates). This alteration is optional. The implementation of the alteration is conditional to a valid API GMP certificate.	2, 3, 4, 13, 14	Immediate implementation. Requires individual filing.
Documentation			
1	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 post-marketing authorization petition.		
2	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 good manufacturing practices audits conducted pursuant to the Collegiate Board Resolution – RDC that provides for the general guidelines for good manufacturing practices of medicinal products.		
3	Expedient number of the API GMP certificate request, according to the Collegiate Board Resolution – RDC that provides for the certification of good API manufacturing practices. For alterations "1d", "1e", "1j", and "1k", the document applies only to the alteration associated to a new manufacturing site.		

4	When there is a DIFA confidentiality restriction, statement from the technically responsible person of the marketing authorization holder or person designated by him/ her that the marketing authorization petitioner has possession of the open part.
5	The impact of the alteration on the medicinal product must be assessed and the evidence to be presented must be determined. If the equivalence of the physical properties and the impurities profile of the API is not demonstrated, tests must be carried out with the medicinal product, proportionally to the potential impact of the alteration. Factors to be considered include characteristics of the API (e.g. SCB classification, occurrence of polymorphism, particle size distribution, morphology) and the relevance of such properties to the medicinal product performance (e.g. pharmaceutical form, release system, manufacturing process). When the technical report of the medicinal product relative bioavailability/ bioequivalence study is submitted, alteration "1e", "1h", or "1k" must be filed.
6	Certificates of analysis issued, or API batch analysis carried out by the API manufacturer(s) (1 batch in the condition approved and 1 batch in the condition proposed).
7	Certificates of analysis issued, or API batch analysis carried out by the medicinal product manufacturer (1 batch in the condition approved and 1 batch in the condition proposed).
8	Assessment of the comparative profile of impurities between the approved and the proposed conditions, including the verification of the need for an impurities' qualification trial.
9	Validation report of the API quality control analytical methods, carried out by the medicinal product manufacturer, where applicable.
10	Validation report of the medicinal product quality control analytical methods, where applicable.
11	Report of the stability study of a batch of the medicinal product. If the alterations in the API quality attributes or impurity profile do not impact the medicinal product stability, the stability study protocol of the first industrial batch of the medicinal product may be submitted, upon technical justification.
12	Documentation regarding the DIFA alteration, according to Annex II of the Collegiate Board Resolution – RDC establishing the DIFA (disregarding the column "Type of alteration"). For alterations for which the column "documents" is not filled or those not provided for in Annex II of the Collegiate Board Resolution – RDC establishing the DIFA, the documentation must be compatible with the nature and complexity of the alteration, considering: 1. Sections of the API documentation directly altered by the alteration; and 2. Sections of the API documentation where evidence must be included to support the alteration.

13	CADIFA or revised CADIFA, with the access statement completed by the DIFA holder on behalf of the medicinal product marketing authorization holder. If the DIFA alteration can be implemented due to deadline expiration, the revised CADIFA does not have to be submitted in the medicinal product post-marketing authorization petition.
14	Statement signed by the technically responsible person of the medicinal product marketing authorization holder, stating that the quality level of the API is the same for which the CADIFA was issued. Quality level is understood as all the information related to manufacturing (manufacturing process, synthesis route), quality control, and packaging.

ANNEX II

1. ALTERATIONS RELATED TO THE ACTIVE PHARMACEUTICAL INGREDIENT

The company responsible for one or more steps of the API manufacturing is considered as manufacturer of API or API manufacturing site. The API manufacturer(s) has/ have the option to send directly to Anvisa, within 30 (thirty) days after filing, the documentation related to the API, duly identified with the process number and expedient to which it relates.

Alterations	Conditions	Documents	Type of petitioning
a. alteration in corporate name of the API manufacturing site	There must be no alteration in the manufacturing unit besides the corporate name.	1	Immediate implementation. Requires individual filing.
b. replacement or inclusion of API manufacturing site of the same pharmochemical group	Synthesis route, production process, batch size, starting material, intermediates, reagents, solvents, and API specifications must remain unaltered.	2, 3, 4, 5, 6, 7, 8, 9, 10	Immediate implementation. Requires individual filing.
c. replacement or inclusion of new API manufacturer	Alterations in the API production process are allowed concomitantly. These include cases of replacement or inclusion of API manufacturing site of the same pharmochemical group, when it does not fit in the specific subject of item "b".	2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 17	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
d. minor alteration in the API production	There must be no significant alteration in the qualitative and quantitative profile of impurities (no new		

	impurities above 0.10%, no alteration in the total limit of impurities approved and residual solvents within the limits adopted in official compendia), as well as alterations in physicochemical properties. The synthesis route must remain unaltered, i.e. the intermediates remain the same and there are no new reagents, catalysts, or solvents used in the process. The specifications of the active substance or intermediates must remain unaltered.	4, 5, 6, 7, 10, 14, 16	Immediate implementation. It does not require individual filing. HMP.
e. major alteration in API production	It refers to alterations that do not fall within the conditions of minor alteration in the API production (item "d").	4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17	It requires individual filing. It must await a favorable manifestation from Anvisa for implementation.
f. alterations made by the API manufacturer	It refers to any inclusion, change, replacement, or exclusion of tests, specifications, and analytical methods made exclusively by the API manufacturer.	18, 19, 20, 21, 22	Immediate implementation. It does not require individual filing. HMP.
Documentation			
1	Statement by the API manufacturing company informing that only the corporate name has been altered.		
2	List containing names and addresses of the companies involved in the different manufacturing steps, including particle size reduction, quality control, and API stability.		
3	Copy of the Good Manufacturing and Control Practices (GMCP) Certificate issued by Anvisa for the active pharmaceutical ingredient, object of the marketing authorization, or copy of the inspection request protocol for the purpose of issuing the GMCP Certificate, provided that the latest inspection was satisfactory. In cases of APIs not included in the list of marketing authorization priorities and with international manufacturing, this document may be replaced by a Copy of the document evidencing compliance with Good Manufacturing Practices issued by the health authority of the country of origin.		
4	Statement that the API process validation has been carried out.		
5	Analytical physicochemical and microbiological quality control reports issued by the API manufacturer related to 1 (one) batch manufactured in the condition approved and 1 (one) batch		

	manufactured in the condition proposed, including data on the impurities profile, particle size distribution and limits, and polymorphic forms.
6	Analytical physicochemical and microbiological quality control reports of the API issued by the medicinal product manufacturer related to 1 (one) batch manufactured in the condition approved and 1 (one) batch manufactured in the condition proposed, including data on the impurities profile, particle size distribution and limits, and polymorphic forms.
7	Analytical physicochemical and microbiological quality control reports of the medicinal product related to 1 (one) batch produced with the API manufactured in the condition approved and 1 (one) batch produced with the API manufactured in the condition proposed.
8	Validation report of the API quality control analytical methods, carried out by the medicinal product manufacturer.
9	Validation report of the medicinal product quality control and stability analytical methods.
10	Stability study protocol regarding the first industrial batch or stability study report related to 1 (one) industrial batch of the medicinal product.
11	Stability study report related to 1 (one) batch of the medicinal product. For replacement or inclusion of a new manufacturer of the API (item "c"), when there is no alteration in the synthesis route, production process, batch size, starting material, intermediates, reagents, solvents, API specifications, impurity qualitative and quantitative profile, particle size distribution, and crystalline form (polymorphism), including solvates and hydrates, this test may be replaced by a stability study protocol regarding the first industrial batch.
12	Technical report containing the following information on the API: a) nomenclature: Brazilian Common Name (DCB); b) structure: structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass; c) physicochemical properties: physical form of the salt, stoichiometric relation between the chemical form of the API presentation and its pharmacodynamically active component, melting point, solubility, particle size, and pKa; d) name of the API manufacturer(s) and their respective address(es); e) document from the official health authority of the country of origin informing the activities authorized for the manufacturer or statement of the API manufacturer stating that the country of origin does not have such document; f) description of the synthesis process: flowchart of the synthesis process, including molecular formula and chemical structures of starting materials and intermediates, with their respective nomenclatures, solvents, catalysts, reagents, and the API, contemplating stereochemistry; g) elucidation of the structure and other characteristics and impurities: confirmation of the structure based on the synthesis route and spectral analysis, contemplating 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, discriminating their characteristics and other polymorphs related to the API and their characteristics, and information on impurities; h) description of the tests, specification limits, and quality control methods of the API, accompanied by validation report of the analytical methods; i) API stability study report containing a summary of the types of studies conducted and the results, in accordance with specific legislation in force, including the results of forced degradation studies and stress conditions and their respective analytical procedures, as well as the conclusions on shelf life or retest period, and j) description of the primary packaging material.
13	Assessment of the comparative profile of impurities (between the approved and the proposed conditions), including the verification of the need for an impurity qualification study.
14	Comparative dissolution profile between the currently approved and the proposed condition. For pharmaceutical forms in which the dissolution profile is not applicable, submit an *in vitro* performance test comparative between the currently approved and the proposed condition. For alterations "c" and "e", the comparative dissolution profile and other *in vitro* performance tests must be performed between the proposed condition and the reference medicinal product.
15	Technical report of the medicinal product relative bioavailability/ bioequivalence study. When there are no alterations in the API physicochemical properties with potential impact on bioavailability, this test may be waived.
16	Technical report containing description of the synthesis route and the API manufacturing flowchart, highlighting the proposed alteration and respective controls of the manufacturing process critical steps.
17	Photostability study report.
18	API manufacturer's justification for specifications, when not compendial.
19	Copy of new specification and/ or new analytical method issued by the API manufacturer.
20	Analytical report issued by the API manufacturer for 1 (one) batch analyzed with the new specification, the new method, or the new test.
21	Validation report of the analytical method issued by the API manufacturer.
22	Justification of the medicinal product manufacturer for not performing the alteration in its quality control, where applicable.