COLLEGIATE BOARD RESOLUTION – RDC NO. 359 OF 27 MARCH 2020

Establishes the Active Pharmaceutical Ingredient Dossier (DIFA) and the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA).

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.

TITLE I

INITIAL PROVISIONS

Article 1. This Resolution establishes the Active Pharmaceutical Ingredient Dossier (DIFA, in Portuguese) and the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA, in Portuguese).

CHAPTER I

SCOPE

Article 2. This Resolution applies to active pharmaceutical ingredients (APIs) used in the manufacture of new, innovative, generic, and similar medicinal products.

Paragraph 1. This Resolution does not apply to atypical API and the API used in the formulation of a pharmaceutical product notified or classified as a biological product, herbal medicinal product, or traditional herbal product, specific medicinal product, or dynamized medicinal product.

Paragraph 2. Additionally, this Resolution does not apply to the API referred to in Paragraph 1 used in association with synthetic or semisynthetic API of products classified as a new, innovative, generic, or similar medicinal product.

CHAPTER II

DEFINITIONS

Article 3. Within the scope of this Resolution, the following definitions are adopted:

I – Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA, in Portuguese): administrative instrument that attests DIFA's adequacy to this Resolution;

II – CADIFA holder: DIFA holder after CADIFA granting;

III – DIFA holder: company that holds the knowledge about the entire manufacturing process of the Active Pharmaceutical Ingredient (API) and under whose responsibility the API is manufactured, from the introduction of the starting material;

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

V – active pharmaceutical ingredient (API): any substance introduced into the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient, and may exert pharmacological activity or another direct effect on the diagnosis, cure, treatment, or prevention of a disease, and may also affect the structure and functioning of the human organism;

VI – expression of interest: an instrument that demonstrates the DIFA's holder interest in obtaining the CADIFA in a way not associated with the petition for marketing authorization or post-marketing authorization of a medicinal product; and

VII – new chemical entity: API used in the formulation of a new medicinal product.

Sole paragraph. In a complementary way, the definitions of the ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) guides to which this Resolution refers and the other ANVISA regulations are also adopted.

TITLE II

ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA) AND THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER ADEQUACY LETTER (CADIFA)

CHAPTER I

SUBMISSION OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA) AND ITS ALTERATIONS

Article 4. The Active Pharmaceutical Ingredient Dossier (DIFA) or its alterations must be sent to ANVISA by its holder.

Sole paragraph. ANVISA, at its discretion, may request the submission of the DIFA, in the following cases:

I – after prior expression of interest by the DIFA holder; or

II – after a public invitation from the Collegiate Board.

Article 5. After DIFA submission pursuant to Article 4, a reference number will be generated.

CHAPTER II

ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Article 6. The DIFA must contain version and index, and have the documents organized in the order in which they are described in Chapter III (Administrative Documents of the Active Pharmaceutical Ingredient Dossier) and Chapter IV (Quality Documents of the Active Pharmaceutical Ingredient Dossier) of this Resolution.

Article 7. The analysis of the Active Pharmaceutical Ingredient Dossier (DIFA) and its alterations includes the assessment of administrative and quality documents.

Article 8. The requirement, approval, or rejection of the DIFA or its alterations shall be sent directly to its holder.

Sole paragraph. If the DIFA or its alterations are rejected, reconsideration of the decision may be requested pursuant to the Resolution that provides on the procedures related to the filing of administrative appeals in the light of ANVISA's decisions.

CHAPTER III

ADMINISTRATIVE DOCUMENTS OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Article 9. The Active Pharmaceutical Ingredient Dossier (DIFA) must contain the following administrative documents:

I – completed API form and statements containing the responsibilities of the DIFA holder with ANVISA and with the petitioner or holder of the marketing authorization of the medicinal product; and

II – assessment by the DIFA holder of the risk of transmission of transmissible spongiform encephalopathy or, where applicable, a declaration that raw materials of human or animal origin are not used.

CHAPTER IV

QUALITY DOCUMENTS OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Article 10. The sections of the DIFA quality documentation must be structured according to the quality module of the active pharmaceutical ingredient (3.2.S) of the Guide for Organization of the Common Technical Document (CTD) for Marketing Authorization and Post-marketing Authorization of Medicinal Products issued by ANVISA.

Paragraph 1. When there is a confidentiality restriction between the DIFA holder and the medicinal product marketing authorization petitioner, the quality documentation must be divided into an open and a restricted part, according to the table in Annex III of this Resolution.

Paragraph 2. The open part must contain enough information to allow the medicinal product marketing authorization petitioner/ holder to assess the quality of the API and its adequacy for manufacturing the medicinal product.

Article 11. The Active Pharmaceutical Ingredient Dossier (DIFA) must meet, as relevant, the guidelines of the following ICH guides and their complementary documents:

I – ICH Q1A – Stability Studies of Active Pharmaceutical Ingredients and Medicinal Products;

II – ICH Q1B – Stability Studies: Photostability Studies of Active Pharmaceutical Ingredients and Medicinal Products;

III – ICH Q1D – Grouping and Matrixing for Stability Studies of Active Pharmaceutical Ingredients and Medicinal Products;

IV – ICH Q1E – Assessment of Stability Results;

V – ICH Q2(R1) – Validation of Analytical Procedures;

VI – ICH Q3A(R2) – Impurities in New Active Pharmaceutical Ingredients;

VII – ICH Q3C(R6) – Impurities: Guide for Residual Solvents;

VIII – ICH Q3D(R1) – Guide for Elemental impurities, pursuant to ANNEX I of this Resolution;

IX – ICH Q6A – Tests and Acceptance Criteria for New Pharmaceutical Ingredients and New Medicinal Products: Chemical Substances;

X – ICH Q11 – Development and Manufacture of Active Pharmaceutical Ingredients (Chemical Entities and Biotechnological/ Biological Entities); and

XI – ICH M7(R1) – Assessment and Control of DNA Reactive Impurities (Mutagenic) in Medicinal Products to Limit Potential Carcinogenic Risk.

Article 12. ANVISA may require tests and documents not provided for in this Resolution, provided that they are based on issues related to the safety and quality of the API and in accordance with international guides.

Article 13. Technical approaches other than those provided for in this Resolution must be technically and scientifically justified.

Section I

General Information (3.2.S.1)

Subsection I

Nomenclature (3.2.S.1.1)

Article 14. The Brazilian Common Name (DCB) or International Nonproprietary Name (INN), chemical name, CAS registration number, compendial name and, if applicable, other relevant names must be presented.

Subsection II

Structure (3.2.S.1.2)

Article 15. Structural formula with stereochemical configuration, molecular formula, and relative molecular mass must be presented.

Subsection III

General Properties (3.2.S.1.3)

Article 16. A list of physicochemical properties and other relevant properties must be presented, especially those that affect the efficacy and safety of the medicinal product, such as solubility, pKa, polymorphism, isomerism, partition coefficient (logP), permeability, and hygroscopicity.

Section II

Manufacturing (3.2.S.2)

Subsection I

Manufacturer(s) (3.2.S.2.1)

Article 17. The corporate name, address, and responsibility of the units responsible for the manufacturing steps of intermediaries and API, as well as API quality control, from the introduction of the starting material(s) must be informed.

Sole paragraph. The units responsible for physical steps (grinding, micronization, lyophilization) and sterilization must be included, when those steps are carried out under the responsibility of the DIFA holder, as well as subcontracted companies.

Subsection II

Description of the Manufacturing Process and In-Process Controls (3.2.S.2.2)

Article 18. A diagram of the synthesis route or process for obtaining the API, from the introduction of the starting material(s), must be presented.

Paragraph 1. Starting materials, intermediates, and API must be described with structural formula, stereochemical configuration, molecular formula, and relative molecular mass.

Paragraph 2. Non-isolated intermediates must be included in the diagram of the synthesis route, illustrated between brackets.

Paragraph 3. Solvents, reagents, catalysts, and other raw materials used in the process must be described, and the steps in which they are used must be indicated.

Article 19. Sequential narrative of the manufacturing process must be presented, including:

I – process parameters, including quantities or bands of raw materials, starting materials, intermediates, solvents, catalysts, and reagents used in the manufacture of industrial scale batches, and operating conditions (e.g. temperature, pressure, pH, time, flow, etc.);

II – identification of critical steps and in-process controls; and

III – batch size and yield information of the process steps.

Article 20. A flowchart of the manufacturing process must be presented, containing a sequence of unit operations, indicating the input and output of materials and in-process controls.

Article 21. If reprocess is routinely used, the procedure and circumstances in which it is used must be described.

Article 22. If solvents or other recovered materials are used, the maximum proportion used must be indicated, and the steps from which they are recovered and those where they are reintroduced must be indicated.

Article 23. Alternative processes with substantially different synthesis routes must constitute distinct DIFAs, even if the specification and impurities profile of terminal intermediates and API are maintained.

Article 24. If mother waters are reused, the information must be included in the sequential narrative of the manufacturing process.

Article 25. Rework procedures should not be included in the DIFA.

Article 26. For sterile API, a description of the sterilization process must be presented.

Article 27. In the case of API obtained directly by fermentation or in which the substance isolated from the subsequent fermentation process or intermediate does not meet the requirements for defining synthetic API starting material, the following information regarding the fermentation process must be presented:

I – description of the manufacturing process;

II – source and type of microorganism;

III – procedures and controls for the preparation of the master cell bank and the working cell bank;

IV – composition of the culture medium;

V – microbial bioburden control in the fermentation process;

VI – precursors or metabolic substrates, if applicable;

VII – reaction controls (times, temperature, aeration, etc.);

VIII – name and composition of preservatives; and

IX – presence of potential adventitious agents based on the type of microorganisms used (e.g. mycotoxins, enzymes).

Article 28. In the case of API derived from plant raw material where the substance isolated from the subsequent plant raw material or intermediate does not meet the requirements for definition as synthetic API starting material, the following additional information must be presented:

I – description of the botanical species and the part of the plant used for extraction;

II – geographical origin of the plant;

III – if relevant, harvesting time;

IV – information on the use of chemical fertilizers, pesticides, fungicides, etc.;

V – potential sources of contamination; and

VI – process controls and operational conditions.

Subsection III

Raw Material Control (3.2.S.2.3)

Article 29. A list of the raw materials used in the API manufacturing process must be presented.

Sole paragraph. All materials used in the API manufacturing process, such as starting materials, reagents, solvents, catalysts, substrates, adjuvants, and recovered materials, are classified as raw materials.

Article 30. The specifications and analytical methods of all raw materials used in the manufacturing process and, where relevant, batch analysis, must be presented.

Paragraph 1. The quality of the raw materials must be adequate for the intended use.

Paragraph 2. The specifications of solvents or other recovered materials must be justified.

Paragraph 3. If the specification of the recovered material contains acceptance criteria less restrictive than that of the fresh material, there must be proof that the quality of the API obtained by the process in which the recovered material is partially or totally used, is equivalent to that of the API obtained by the process in which the fresh material is used.

Article 31. For starting materials, the following shall be presented:

I – name and chemical structure;

II – specification;

III – analytical methods;

IV – the manufacturers' corporate name and address;

V – synthesis route of each supplier of starting material, including reagents, solvents, and catalysts;

VI – batch analysis; and

VII – justification for selection of the starting material.

Paragraph 1. The specifications of starting materials must be justified and must include, as applicable, tests for specified and unspecified impurities, total impurities, solvents, catalysts, elemental impurities, and mutagenic impurities.

Paragraph 2. For semisynthetic API whose proposed starting material is obtained by fermentation or derived from a substance obtained by fermentation, the justification for selecting the starting material must include a discussion about the carriage of impurities inherent to the fermentation process (e.g. DNA, proteins) up to the API.

Paragraph 3. For semisynthetic API whose proposed starting material is isolated from plant raw material or derived from a substance isolated from plant raw material, the justification for

selecting the starting material must include a discussion about the carriage of impurities inherent to the cultivation processes (e.g. pesticides, heavy metals, aflatoxins) and extraction up to the API.

Paragraph 4. In cases where there is more than one supplier for the same starting material, the specification of the intermediate or API manufacturer for the starting material must be discussed understanding the possible differences between the obtention forms proposed.

Paragraph 5. The technically inadequate justification for selecting the starting materials shall imply a request for redefinition.

Subsection IV

Control of Critical and Intermediate Steps (3.2.S.2.4)

Article 32. Tests and acceptance criteria must be presented, with justification based on experimental data, for the critical steps identified in the sequential narrative of the manufacturing process.

Article 33. The specifications and analytical methods of isolated intermediates must be presented.

Sole paragraph. Intermediate specifications must be justified and must include, as applicable, tests for specified and unspecified impurities, total impurities, solvents, catalysts, elemental impurities and mutagenic impurities.

Article 34. In the case of non-isolated intermediates, the tests and parameters used to determine the end of the chemical reaction must be presented or their absence justified.

Subsection V

Process Validation (3.2.S.2.5)

Article 35. The API manufacturing process, from the introduction of the starting material(s), must be validated prior to commercialization.

Article 36. For sterile API, the following must be presented:

I – justification for choosing the sterilization method; and

II – studies, protocols, and validation reports of sterilization and aseptic processing steps.

Subsection VI

Manufacturing Process Development (3.2.S.2.6)

Article 37. For API classified as a new chemical entity, description and discussion of significant alterations in the API manufacturing process or place involved in the manufacture of batches, must be presented, as applicable:

I – pre-clinical;

II – clinical;

III – scaling up;

IV – pilots; and

V – commercial, if available.

Sole paragraph. For API not classified as a new chemical entity, the DIFA holder may include manufacturing process development data to corroborate the proposed API control strategy.

Article 38. In case of using an approach classified as "Quality by design" for the development of the API manufacturing process, studies carried out to define the "Design space" must be presented.

Sole paragraph. For the API referred to in the caption of this article, the guidelines of the ICH Q8(R2) (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) Guides must be met.

Section III

Characterization (3.2.S.3)

Subsection I

Elucidation of Structure and Other Characteristics (3.2.S.3.1)

Article 39. A characterization of the chemical structure must be presented, based on the proposed synthesis route and appropriate instrumental methods.

Sole paragraph. In the case of API for which there is a pharmacopoeial reference chemical substance (RCS), a comparison of the identification tests between the API and the RCS may be presented.

Article 40. Characterization and discussion of the API solid phase properties must be submitted, as applicable.

Subsection II

Impurities (3.2.S.3.2)

Article 41. A detailed discussion must be presented with all potential impurities arising from the manufacturing process, such as reagents, catalysts, co-products, solvents, and other raw materials, as well as degradation products, including:

I – formation, destination, and elimination; and

II – control and proposal of acceptance criteria.

Paragraph 1. The discussion must include specified and unspecified impurities, total impurities, elemental impurities, mutagenic impurities, and the justification for the absence of unspecified potential impurities in the API specification.

Paragraph 2. Based on risk analysis, a validation of critical parameters for the analytical methods used in the impurities' carriage study must be presented.

Section IV

API Quality Control (3.2.S.4)

Subsection I

Specification (3.2.S.4.1)

Article 42. The API specification must be presented, with a set of tests, references to analytical methods, and acceptance criteria with which the API must comply in order to be considered appropriate for the intended purpose.

Subsection II

Analytical Methods (3.2.S.4.2)

Article 43. The analytical methods used in routine quality control and API stability studies must be presented.

Subsection III

Validation of Analytical Methods (3.2.S.4.3)

Article 44. The validation of the analytical methods used in quality control and stability studies of the API must be presented, in accordance with the Resolution that provides for the validation of analytical methods or ICH Q2 guide (Validation of Analytical Procedures).

Subsection IV

Batch Analysis (3.2.S.4.4)

Article 45. An analysis of at least 3 (three) batches of API manufactured in accordance with the process described and the specification proposed in the DIFA must be presented.

Sole paragraph. For significant variables of the manufacturing process, a batch number analysis must be presented, according to Annex II of this Resolution.

Article 46. For API classified as a new chemical entity, an analysis of the batches referred to in the discussion of Article 37 must be also presented.

Article 47. Batch analysis must contain at least the following information:

I – manufacturing date;

II – batch size and number;

III – manufacturing site; and

IV – results for all tests contained in the specification.

Sole paragraph. Absence of tests provided for in the proposed specification or unexpected results must be justified.

Subsection V

Specification Justification (3.2.S.4.5)

Article 48. A justification for the API specification must be presented.

Article 49. The justification for the API specification may be based, as applicable, on:

I – pre-clinical and clinical studies;

II – impurity qualification studies;

III – results of batch analysis;

IV – monographs of official compendia acknowledged by ANVISA, according to the Resolution that provides for the admissibility of foreign pharmaceutical codes;

V – in-process control data, control of intermediaries, and critical steps;

VI – studies of carriage of impurities; and

VII – guides listed in Article 11 of this Resolution.

Section V

Reference Materials and Chemical Substances (3.2.S.5)

Article 50. Information on reference and working materials and chemical substances must be presented.

Section VI

Packaging (3.2.S.6)

Article 51. Description and specification of the packaging materials must be presented.

Paragraph 1. For functional secondary packaging, information relevant to its function must be presented.

Paragraph 2. For non-functional secondary packaging materials, a simplified description must be presented.

Paragraph 3. The primary packaging material specification must include an identification test and description.

Article 52. A discussion of the following attributes of packaging materials must be presented, as applicable:

I – protection from light;

II – protection from moisture;

III – compatibility between primary packaging material and API, including the possibility of sorption or leaching of impurities that impact the API quality, for liquid API; and

IV – compliance with the requirements for packages and materials intended for having contact with food.

Section VII

Stability (3.2.S.7)

Subsection I

Stability Summary (3.2.S.7.1)

Article 53. Summary of the studies conducted, the protocols used, and the results obtained must be presented, in accordance with the Resolution establishing the criteria for carrying out stability studies of active pharmaceutical ingredients.

Sole paragraph. The storage conditions and the proposal for a retest period or shelf life must be contemplated in the conclusion.

Subsection II

Post-Submission Protocols and Commitments (3.2.S.7.2)

Article 54. Follow-up stability study protocols must be presented, in accordance with the Resolution establishing the criteria for carrying out stability studies of active pharmaceutical ingredients.

Article 55. In the case of a proposed provisional retest period or shelf life, based on extrapolation, a statement that stability studies shall be completed with the aim of confirming or reviewing the API retest period or shelf life must be presented.

Subsection III

Stability Data and Reports (3.2.S.7.3)

Article 56. The results of the stability studies conducted in accordance with the Resolution establishing the criteria for carrying out stability studies of active pharmaceutical ingredients must be presented.

CHAPTER V

DIFA LIFECYCLE

Article 57. The DIFA holder must submit DIFA amendments to ANVISA, according to the conditions and supporting documentation of ANNEX II of this Resolution.

Paragraph 1. DIFA amendments may be classified as:

I – annual notification;

II – immediate notification;

III – minor; or

IV – major.

Paragraph 2. DIFA amendments not provided for in ANNEX II must be classified as minor.

Paragraph 3. In the case of amendments for which the column "documents" is not filled or those that fall within Paragraph 2, the supporting documentation must be compatible with the nature and complexity of the amendment, considering:

I – DIFA sections directly altered by the amendment; and

II – DIFA sections in which evidence must be included to support the amendment.

Article 58. After approval of the amendment, ANVISA shall issue a revised CADIFA in the following cases:

I – notification and minor amendments that alter the contents of the CADIFA; or

II – major amendment, regardless of the alteration in the contents of the CADIFA.

Article 59. The DIFA holder must inform the medicinal product marketing authorization petitioner or holder about amendments subject to regulatory approval or not, where required by good manufacturing practices or quality agreements.

Section I

Submission of Amendments

Article 60. The DIFA holder must submit to ANVISA, at each amendment:

I – amendment form; and

II – supporting documentation.

Article 61. Amendments associated with or arising from other amendments must be submitted jointly, prevailing the classification of the greatest risk amendment.

Section II

Classification of Amendments

Article 62. Annual notification and immediate notification amendments do not depend on ANVISA’s prior knowledge or manifestation to be implemented.

Article 63. Annual notification amendments must be filed within 12 months from the date of implementation.

Article 64. Immediate notification amendments must be filed shortly after the date of implementation.

Article 65. Minor and major amendments must await Anvisa's manifestation to be implemented.

Sole paragraph. If Anvisa does not issue an opinion within 60 (sixty) days from receipt of the documentation, for minor amendments, or 180 (one hundred and eighty) days, for major amendments, the amendment may be implemented.

Article 66. The implementation of the amendment does not preclude its analysis, at any time, and Anvisa may request additional evidence, ratify, or reject the amendment.

Sole paragraph. In case of rejection, the conditions prior to the amendment(s) must be restored immediately after Anvisa's manifestation.

CHAPTER VI

ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER ADEQUACY LETTER (CADIFA)

Article 67. If the DIFA is approved, Anvisa shall issue the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA) to the DIFA holder.

Sole paragraph. When issued pursuant to the sole paragraph of Article 4, the corporate name of the DIFA holder, DIFA version, CADIFA number, and its status will be published on Anvisa's website.

Article 68. The following shall be included in the CADIFA:

I – CADIFA number and date of issue;

II – API name, DCB number, and Chemical Abstracts Service (CAS) number;

III – DIFA holder corporate name and address;

IV – corporate name and address of the manufacturing sites;

V – API specification and, if applicable, a compendial reference;

VI – description of the packaging;

VII – API storage conditions;

VIII – API retest period or shelf life; and

IX – field for access declaration.

Paragraph 1. The CADIFA may contain other information deemed relevant.

Paragraph 2. The information in item IV shall include:

I – API and intermediates manufacturing sites; and

II – sites of sterilization or physical stages (micronization, grinding, sieving, and lyophilization), when performed under the responsibility of the DIFA holder.

Article 69. Manufacturers must comply with the good manufacturing practices for active pharmaceutical ingredients.

Sole paragraph. The CADIFA will not be issued if non-compliance with the good manufacturing practices is found.

CHAPTER VII

SUSPENSION AND CANCELLATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER ADEQUACY LETTER (CADIFA)

Article 70. CADIFA suspension and cancellation shall be notified to the DIFA holder and to the petitioners and holders of marketing authorization of medicinal products associated with the CADIFA.

Sole paragraph. In cases where the CADIFA is issued pursuant to the sole paragraph of Article 4 of this Resolution, its suspension and cancellation shall be published on Anvisa's website.

Section I

Suspension of the CADIFA

Article 71. The CADIFA may be suspended as a result of:

I – health inspection conducted by the Brazilian National Health Surveillance System (SNVS) or by entities with which Anvisa has cooperation agreements that detect critical or major non-conformities and lead to the conclusion that the API manufacturing process is carried out in disagreement with the good manufacturing practices, and may cause health risk;

II – finding that the API is manufactured in disagreement with the DIFA;

III – no re-establishment of the previously approved conditions, in case of rejection of amendments already implemented without prior assessment by Anvisa;

IV – non-compliance with technical adjustments arising from commitments made prior to granting the CADIFA; or

V – refusal to receive health inspection.

Paragraph 1. The CADIFA shall have the suspension revoked after proof of adequacy to the regulations in force, to the requirements or requests issued by Anvisa or, where applicable, by entities with which Anvisa has cooperation agreements.

Paragraph 2. Anvisa may suspend the CADIFA, for reasons not provided for in this Resolution, in a preventive and duly justified manner, in order to avoid exposure of the population to health risk.

Article 72. The CADIFA may be suspended at the request of the DIFA holder, due to the impossibility of complying with any regulatory requirement.

Paragraph 1. The suspension period may not exceed 2 (two) years, except upon justification proposed by the holder and accepted by Anvisa.

Paragraph 2. The DIFA holder is responsible for requesting reactivation of the CADIFA.

Article 73. CADIFA suspension may result in the suspension of the importation of the API manufactured abroad, or the manufacture of the API manufactured in Brazil, or the API commercialization.

Article 74. CADIFA suspension may result in the suspension of the manufacture, import, or commercialization of medicinal products linked to the suspended CADIFA.

Section II

CADIFA Cancellation

Article 75. The CADIFA may be cancelled as a result of:

I – health inspection conducted by SNVS or by entities with which Anvisa has cooperation agreements that detect critical or major non-compliances and lead to the conclusion that the API manufacturing process is carried out in disagreement with the good manufacturing practices, and may cause serious health risk;

II – finding that the API is manufactured in disagreement with the DIFA, and may cause serious health risk;

III – finding of false information for granting or maintaining the CADIFA;

IV – recurrence of items that led to CADIFA suspension;

V – non-compliance with Anvisa requests and requirements after CADIFA suspension;

VI – cessation of the DIFA holder activities or the API production; or

VII – the course of 2 (two) years of CADIFA suspended on request, except in the case provided for in Paragraph 1 of Article 72.

Sole paragraph. Anvisa may cancel the CADIFA, for reasons not provided for in this Resolution and duly justified, in order to avoid exposure of the population to serious health risk.

Article 76. The CADIFA may be cancelled at the request of the DIFA holder.

Article 77. CADIFA cancellation, due to health reasons, shall result in suspension of the import of API manufactured abroad, or the manufacture of API manufactured in Brazil, or the API commercialization.

Article 78. The cancellation of CADIFA may result in the suspension of the manufacture, commercialization, or import of medicinal products linked to the cancelled CADIFA.

TITLE III

FINAL AND TRANSITIONAL PROVISIONS

Article 79. The manufacturers of the APIs listed below, which have not been regularized pursuant to the Collegiate Board Resolution – RDC No. 57 of 17 November 2009, shall be excluded from the processes of medicinal products in which they are approved.

Paragraph 1. The provisions in the caption of this article 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 – di-hydrate 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.

Paragraph 2. The medicinal product in whose marketing authorization process there is not an approved API manufacturer left shall have its manufacture suspended until the inclusion of a new manufacturer.

Article 80. 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 81. On 1 March 2021, the following shall be revoked:

I – Collegiate Board Resolution – RDC no. 57 of 17 November 2009;

II – Normative Instruction no. 15 of 17 November 2009;

III – Normative Instruction no. 3 of 28 June 2013;

IV – Joint Technical Note 01/2016 – COIFA/ GGMED – COINS/ GIMED of 22 April 2016; and

V – Technical Note no. 06-001/2015 – COISC/ GGINP/ SUINP/ ANVISA – COIFA/ GGMED/ SUMED/ ANVISA.

Article 82. This Resolution comes into force on 3 August 2020.

ANTONIO BARRA TORRES

ANNEX I – IMPLEMENTATION OF THE ICH Q3D GUIDE BY THE DIFA HOLDER

Irrespective of the provisions of this Annex, specific tests for elemental impurities contained in the adopted monograph must be included in the API specification, except if their absence is properly justified.

In cases of DIFA submitted pursuant to the sole paragraph of Article 4, there shall be no conclusion on the suitability of the proposed acceptance criteria. This assessment shall be carried out in the context of the assessment of the medicinal product marketing authorization or post-marketing authorization petition.

When the risk assessment of elemental impurities of the API has been carried out in an integrated manner with that of the medicinal product, in accordance with ICH Q3D guide,

compliance with the requirements in items 1 and 2 shall be excused. In other cases, the DIFA holder is allowed to adopt one of the following strategies:

1 With risk analysis summary (RAS):

The option for this strategy must be stated in the DIFA.

The RAS must be presented, preferably, in the subsection of impurities and must detail the fundamentals for carrying out the study, as well as include a justification for the control strategy adopted after the risk assessment. When there is a confidentiality restriction, the RAS Table of this Annex must be filled, made available in the open part of the DIFA, and included in the RAS.

If the RAS is deemed insufficient, it shall be considered that the manufacturer opted for the strategy without RAS.

1.1 Requirements

In addition to the principles of ICH Q3D Guide, the DIFA holder must be attentive to the following instructions when opting for the RAS strategy:

a) How to prepare the RAS:

The RAS shall consider all possible sources of contamination, including elemental impurities intentionally introduced in the manufacturing process after the introduction of starting materials, as well as contamination from raw materials (e.g. starting materials, reagents, water), packaging equipment and materials.

The route of administration, which determines the basis for discussion of the risk analysis, must be compatible with that of the medicinal product.

The RAS must consider the 24 elemental impurities described in Table 5.1 of ICH Q3D guide, which means that:

o Class 1 and 2A elements, as well as elements intentionally introduced into the manufacturing process, regardless of Class, must be discussed systematically.

o If relevant, depending on the API use, Class 3 elements must be discussed.

o A justification of why specific elemental impurities were included in the scope of the RAS is considered as relevant information and must be included.

b) How to define the control strategy:

The control strategy must focus on the absence of elemental impurities in the API based on process capacity and control of elemental impurities, preferably using option 1 or, alternatively, the acceptance criterion established based on the allowed daily exposure and maximum daily dose.

The absence of an elemental impurity is understood when it is shown that it is eliminated at a concentration consistently below 30% of the proper acceptance criterion, taking into account the route of administration, in at least 3 consecutive commercial batches or 6 consecutive pilot scale batches.

Where applicable, appropriate test and acceptance criterion for elemental impurities in the API must be included in the API specification. For all elemental impurities introduced in the last stage of the manufacturing process, considering that there is a high risk of being carried to the API, a

test must be included, unless consistently demonstrated and convincing that the process is capable of eliminating the impurity at a concentration below 30% of the appropriate acceptance criterion.

A multi-batch screening can be used to support the RAS, but it does not replace it. This can be performed similarly to the illustration in appendix 4 of ICH Q3D Guide.

Regarding analytical methods:

For screening methods, the analytical technique must be mentioned, and minimum validation information must be presented, such as specificity and detection and quantification limits.

For methods that integrate the API specification, detailed description of the method must be presented. Validation must be performed in accordance with Subsection III – Validation of Analytical Methods of this Resolution.

c) RAS table

The table below containing the RAS conclusion must be included in the DIFA.

The purpose of the table is to contain information about the API contamination level, so that the medicinal product marketing authorization petitioner or holder can implement ICH Q3D guide by the approach of the components of the finished product.

RAS table				
Intended route of administration / Use of the API:				
Element	Class	Intentionally introduced?	Considered in the risk analysis?	Conclusion
Cd	1	*	Yes	**
Pb	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2A	*	Yes	**
V	2A	*	Yes	**
Ni	2A	*	Yes	**
T1	2B	*	*	**
Au	2B	*	*	**
Pd	2B	*	*	**
Ir	2B	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**

Mo	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Cr	3	*	*	**

* Yes / No
** The following statements may be used, as provided in item 1.1:
– "Absent", which means, for example, "concentration below 30% of the acceptance criterion by Option 1 of ICH Q3D Guide or "concentration below X ppm";
– or "< X ppm";
– or "There is no identified risk".

It is recommended not to include individual results of batch analysis in the table. The DIFA holder must ensure that the concentration of elemental impurity is below the maximum level indicated.

2 Without risk analysis summary

2.1 Requirements

If the strategy without RAS is chosen, the DIFA holder must be attentive to the following instructions:

The DIFA holder must declare all elemental impurities, regardless of class, intentionally introduced into the API manufacturing process after introducing the starting materials. It must also submit data demonstrating its levels in the API.

For all the elemental impurities introduced in the last stage of the manufacturing process, considering there is a high risk of being carried to the API, a test must be included, unless consistently and convincingly demonstrated that the process is capable of eliminating the impurity at a concentration below 30% of the appropriate acceptance criterion. Preferably, option 1 of ICH Q3D Guide must be adopted or, alternatively, the acceptance criterion established based on the allowed daily exposure of ICH Q3D Guide and maximum daily dose.

The accepted criteria proposed for the control of elemental impurities must reflect the process capacity. The allowed daily exposures of ICH Q3D Guide may be used as a reference.

A detailed description of the analytical method, which shall be attached to the CADIFA, must be submitted. Validation must be performed according to Subsection III – Analytical Methods Validation of this Resolution.

ANNEX II – AMENDMENTS, CONDITIONS, AND MINIMUM SUPPORTING DOCUMENTATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER

1 – Administrative Amendments

1.1 Alteration of the corporate name and/ or designation of the CADIFA holder address	Conditions	Documents	Type of amendment
	1	1, 2	Immediate notification

Conditions
1. The CADIFA holding legal entity must be maintained (except in cases of sale or merger of the company).
Documents
1. Formal document of an official organism in which the new corporate name and/ or new address are mentioned. 2. Updated statements of item I of Article 9 of this Resolution.

1.2 Alteration in corporate name and/ or designation of the API manufacturing site or quality control address	Conditions	Documents	Type of amendment
	1	1, 2	Immediate notification

Conditions
1. The manufacturing site and quality control must remain the same.
Documents
1. Formal document of an official organism in which the new corporate name and/ or new address are mentioned. 2. Statements that the API manufacture is carried out in accordance with the DIFA and the good manufacturing practices, and that the manufacturer is willing to be inspected (Article 9, item I).

1.3 Alteration in corporate name and/ or address designation of the manufacturer of the starting material used in the API manufacture	Conditions	Documents	Type of amendment
	1	1	Annual notification

Conditions
1. The manufacturing site must remain the same.
Documents
1. Updated list (with full company name and address) of approved and proposed starting material manufacturers.

1.4 Alteration in corporate name and/ or address designation of the manufacturer of the intermediate used in the API manufacture	Conditions	Documents	Type of amendment
	1	1, 2	Immediate notification

Conditions
1. The manufacturing site must remain the same.
Documents
1. Updated list (with full company name and address) of approved and proposed manufacturers of intermediates. 2. Statements that the API manufacture is carried out in accordance with the DIFA and the good manufacturing practices, and that the manufacturer is willing to be inspected (Article 9, item I).

1.5 Exclusion of intermediate manufacturing site or API manufacturing or quality control site	Conditions	Documents	Type of amendment
	1	1, 2	Immediate notification

Conditions
1. There must be at least one more site/ manufacturer, among those previously stated, responsible for the same activity as that excluded.
Documents
1. Justification for exclusion. 2. Updated list (with full corporate name and address) of proposed and approved sites.

1.6 Exclusion of the manufacturing site of the starting material used in the API manufacture	Conditions	Documents	Type of amendment
	1	1, 2	Annual notification

Conditions
1. There must be at least one more site/ manufacturer, among those previously stated, responsible for the same activity as that excluded.
Documents
1. Justification for exclusion. 2. Updated list (with full corporate name and address) of proposed and approved starting material manufacturing sites.

1.7 Amendment in product code or API reference number or any raw material used in its manufacture	Conditions	Documents	Type of amendment
	1	1	Annual notification

Conditions
1. The alteration is not related to the API or raw material quality.
Documents
1. Approved and proposed reference code or number.

2 – Quality Alterations

2.1 Alteration in manufacturer of the starting material used in the API manufacture	Conditions	Documents	Type of amendment
1. The proposed starting material manufacturer is of the same group as the currently approved one.	1, 2	1, 2, 3, 4	Immediate notification
2. The proposed starting material manufacturer is not of the same group as the currently approved one.	1, 2	1, 2, 3, 4	Minor
3. The proposed starting material manufacturer uses a different route of synthesis or different manufacturing conditions which have an impact on the specification of the starting material.		1, 3, 4	Minor
4. The proposed starting material manufacturer uses a different route of synthesis or different manufacturing conditions which have an impact on the specification of the API.			Major (*)

Conditions
1. The specification of the starting material is identical to the approved one. 2. The API is not sterile.
Documents
1. Statement by the DIFA holder that the API specification has not been altered. 2. Statement by the DIFA holder that the specification and analytical methods of the starting material remain the same. If the proposed manufacturer of the starting material adopts a synthesis route other than that approved, the diagram of the synthesis route of the proposed manufacturer must be presented. 3. List (with full corporate name and address) of all approved and proposed starting material manufacturing sites.

4. Batch analysis (in table format) of at least two batches (minimum pilot scale) of the API manufactured with the starting material of approved and proposed manufacturers. *If the API quality characteristics are altered (e.g. physical properties, impurity profile) so that its stability may be compromised, include comparative stability studies between the approved and the proposed conditions.

2.1 Alteration in intermediate manufacturer	Conditions	Documents	Type of amendment
1. The proposed intermediate manufacturer is of the same group as the currently approved one.	1, 2	1, 2, 3, 4, 5	Immediate notification
2. The proposed intermediate manufacturer is not of the same group as the currently approved one.	1, 2	1, 2, 3, 4, 5	Minor
3. The proposed intermediate manufacturer uses a substantially different route of synthesis or manufacturing conditions which possibly impact on the specification (qualitative and/ or quantitative impurity profile) of the API (e.g. alteration in the synthetic strategy, introduction of new reagents, solvents, or raw materials in the synthesis route).	3		Major (*)

Conditions
1. The specification and synthesis route (including in-process controls, methods of analysis of all raw materials) of the intermediate are identical to those approved. 2. The API is not sterile. 3. Where substantially different synthesis route or manufacturing conditions are used, the alteration is allowed only for manufacturer replacement. The inclusion of an alternative process in a dossier with a different synthesis route (i.e. distinct intermediates, even if the API impurity profile is maintained), must constitute a new DIFA.
Documents
1. Statement by the DIFA holder that the API specification has not been altered. 2. Statement by the DIFA holder that the synthesis route/ manufacturing process (or, in the case of API obtained from plant raw material, where appropriate, geographical

origin and production), the specification and analytical methods of the intermediate have not been altered. 3. List (full corporate name and address) of all approved and proposed manufacturing sites. 4. Batch analysis (in table format) of at least two batches (minimum pilot scale) of the API manufactured with the intermediate of the approved and the proposed manufacturers. 5. Statements that the API manufacture is carried out in accordance with the DIFA and the good manufacturing practices, and that the proposed manufacturer is willing to be inspected (Article 9, item I). Information on suppliers and specification of the starting materials of the proposed intermediate manufacturer. *If the API quality characteristics are altered (e.g. physical properties, impurity profile) so that its stability may be compromised, include comparative stability studies between the approved and the proposed conditions.

2.3 Alteration in the API manufacturer (including quality control units)	Conditions	Documents	Type of amendment
1. The proposed API manufacturer (site/ unit) is of the same group as the currently approved one.	1, 2	1, 2, 3, 4	Immediate notification
2. The proposed API manufacturer (site/ unit) is not of the same group as the currently approved one.	1, 2	1, 2, 3, 4	Minor
3. Inclusion or replacement of API quality control site.	2, 3	1	Immediate notification
4. Inclusion or replacement of sterilization site using a standard sterilization method (provided for in pharmacopoeias acknowledged by ANVISA).	1	1, 2, 5	Minor
5. Inclusion of additional micronization site.	1, 2, 4, 5	1, 2, 3, 4	Immediate notification

Conditions
1. The specification (including in-process controls and analytical methods of all raw materials), manufacturing process (including batch size), and detailed synthesis route are identical to the approved ones. 2. The API is not sterile. 3. The transfer of methods has been satisfactorily completed.

4. The particle size distribution specification and its respective method are the same as those already in the CADIFA. 5. There is already an approved micronization site included in the CADIFA.
Documents
1. List (full corporate name and address) of all approved and proposed manufacturing sites. 2. Batch analysis (in table format) of at least two batches (minimum pilot scale) of the API manufactured in the approved and the proposed API manufacturing sites. 3. Statements that the API manufacture is carried out in accordance with the DIFA and the good manufacturing practices, and that the proposed manufacturing site is willing to be inspected (Article 9, item I). Information on suppliers and specification of the starting materials of the proposed manufacturer. 4. Statement by the DIFA holder that the synthesis route/ manufacturing process (or, in the case of API obtained from plant raw material, where appropriate, geographic origin and production), the API specification and analytical methods have not been altered. 5. Statement that sterilization is carried out in accordance with the DIFA and the good manufacturing practices, and that the proposed sterilization site is willing to be inspected (Article 9, item I).

2.4 Alteration in the API or intermediate manufacturer	Conditions	Documents	Type of amendment
1. Minor alteration of intermediate or API manufacturing process that cannot impact the API quality, safety, or control strategy.	1, 2	1, 2, 3	Annual notification
2. Any other minor alterations in the intermediate or API manufacturing process (e.g. introduction of the recovery procedure; addition of solvent in synthetic step other than final purification and when the solvent is already used at another step of the process; alterations in the process resulting in a new degree of API quality, including micronization; alteration of raw material at risk of transmission of transmissible spongiform encephalopathy to raw material of plant, synthetic origin, or with no risk).		1, 2, 4, 5, 6	Minor

3. Replacement of the manufacturing process with substantial alterations that may affect the quantitative and qualitative impurity profile; inclusion of a process without isolation of intermediates; introduction of new technology (e.g. continuous flow chemistry or continuous manufacturing).	3		Major (*)
4. Alteration in sterile API sterilization steps, including batch size.			Major (*)
5. Alteration related to geographical origin or production of API obtained from plant raw material.			Major (*)
Conditions			
1. There is no alteration in the API and intermediate specifications, and there is no adverse alteration in the qualitative and quantitative profile of API impurities. 2. There is no alteration in the synthesis route, i.e., the intermediates are the same and there are no new reagents, catalysts, or solvents used in the process (e.g. non-significant adjustments in operational conditions; non-significant adjustments in equipment; inclusion of a reprocess step, i.e., repetition of an already approved step; repetition of washing and purification steps within the same step; equipment alterations/ improvements, except for sterile API). In the case of API obtained from plant raw material, there is no alteration in geographical origin and manufacturing process. 3. When substantially different synthesis route or manufacturing conditions are used, the alteration is allowed only for replacement of the manufacturing process. The inclusion of an alternative process in a dossier with a different synthesis route (i.e. distinct intermediaries, even if the API impurity profile is maintained), must constitute a new DIFA.			
Documents			
1. Batch analysis (in table format) of at least two batches (minimum pilot scale) of the API manufactured by the approved and proposed processes. 2. Direct comparison between approved and proposed processes. 3. Statement by the DIFA holder that there is no alteration in the API specification.			

4. Specification of the DIFA holder for the proposed supplier raw material. 5. If relevant, the manufacturer's statement that the raw material is of plant, synthetic origin, or with no risk of transmission of TSE (specifying the origin). 6. If relevant, statement from the DIFA holder that there is no alteration in the API manufacturing process and API specification. *If the API quality characteristics are altered (e.g. physical properties, impurity profile) so that its stability may be compromised, include comparative stability studies between the approved and the proposed conditions.

2.5 Alteration in the API or intermediate batch size	Conditions	Documents	Type of amendment
1. Increase of up to ten times in batch size compared to initially approved size.	1, 2, 3, 4, 6, 7	1, 2, 3, 4	Annual notification
2. Reduction in batch size by up to ten times.	1, 2, 3, 4, 5, 6	1, 2, 3, 4	Annual notification
3. Increase of more than ten times in batch size compared to the approved batch size.		2, 3, 5	Minor

Conditions
1. Alterations in the manufacturing process are restricted to those necessary for scaling up or down (e.g. use of equipment of different capacity). 2. Results of at least two batches of the proposed size, demonstrating that they comply with the specification. 3. API is not sterile. 4. The alteration does not affect the reproducibility of the manufacturing process. 5. The alteration must not result from unexpected events that occurred in the manufacturing process or from stability issues. 6. There is no alteration in API and intermediate specifications. 7. The currently approved batch size was not approved through notification.
Documents
1. The number of the proposed size batches that have been tested. 2. Approved and proposed batch size. 3. Updated and complete description of the manufacturing process, specifying the proposed batch size.

4. Statement by the DIFA holder that the alterations in the manufacturing process are restricted to those necessary for scaling up or down, which do not result from unexpected events that occurred during the manufacture or from stability issues, and that there is no alteration in the API or intermediate specifications. 5. Batch analysis (in table format) of at least one batch of approved and proposed sizes.

2.6 Alteration of tests and acceptance criteria of in-process controls used in the manufacture of the API or of acceptance criterion of starting material, reagent, or intermediate	Conditions	Documents	Type of amendment
1. Restriction of acceptance criterion of in-process control used in the manufacture of the API or acceptance criterion of starting material, reagent, or intermediate.	1, 2, 3	1	Annual notification
2. Inclusion of a new in-process control test used in the manufacture of API or test of starting material, intermediate, or reagent.	1, 4, 5, 6	1, 2	Annual notification
3. Inclusion of a new in-process control test related to a critical parameter.		1, 2	Major
4. Exclusion of non-relevant in-process control test, starting material, intermediate, or reagent.	1, 6	1, 3	Annual notification
5. Expansion of acceptance criterion of in-process control test used in the API manufacture or test of starting material, intermediate, or reagent that may have a significant impact on the API quality.			Major
6. Exclusion of in-process control test used in the API manufacture that may have a significant impact on the API quality.			Major
7. Minor method alteration or update.	2, 3, 5, 7	1, 2	Annual notification
8. Alteration in the acceptance criterion of mutagenic impurity in the starting material, intermediate, or reagent, in accordance with the principles and acceptance criteria of ICH M7 guide.		1, 2, 4, 5	Minor
9. Alteration in the biological method, including replacement or inclusion.		1, 2	Minor

Conditions
1. The alteration does not result from unexpected events that occurred in manufacturing.

2. The alteration is within the range of the currently approved acceptance criterion. 3. There is no alteration in the method (e.g. alteration in column length or temperature, but not in column type) or method alterations are minor. 4. Any new method does not involve non-standard methodology or standard methodology used alternatively. 5. The new method is not biological (pharmacopoeial microbiological methods are excluded). 6. The specification parameter is not related to any critical parameters, such as content, impurities (except solvent not used in the API manufacture); controls of mutagenic impurities; controls of elementary impurities; impurities not controlled in other process steps; any physical characteristics (particle size, density, or beat density, identification, water). 7. Validation studies have been conducted and show that the new method is at least equivalent to the approved one.
Documents
1. Comparative table between in-process control tests or acceptance criterion for starting material, intermediate, or reagent. 2. Description and validation of any non-compendial methods, where applicable. 3. Justification/ risk assessment by the DIFA holder for in-process control tests considered not relevant. 4. Justification/ risk assessment by the DIFA holder demonstrating that the excluded or expanded parameter is in accordance with the principles and acceptance criterion of ICH M7 Guide. 5. Analysis of two API production batches with all specification parameters.

2.7 Alteration in API tests and/ or acceptance criteria	Conditions	Documents	Type of amendment
1. Restriction of the API acceptance criterion.	1, 2, 3	1	Immediate notification
2. API test inclusion.	1, 4, 5, 6, 7	1, 2, 3	Immediate notification
3. Exclusion of non-significant API test (e.g. obsolete parameter).	1, 7	1, 4	Annual notification
4. Exclusion of test that may have a significant impact on the API specification.			Major

5. Expansion of the API acceptance criteria according to the compendium already adopted or ICH Guides.		1, 2, 3	Minor
6. Expansion of the approved API acceptance criteria.			Major
7. Alteration of mutagenic impurity acceptance criterion in the API specification according to the principles and acceptance criteria of ICH M7 Guide.		1, 3, 5	Minor
8. Inclusion or revision (non-editorial) of a Risk Analysis Summary of elemental impurities.	8	6	Minor
9. Inclusion of test related to a new quality degree of the API to be included in the CADIFA (e.g. micronized API).		1, 2, 3, 7, 8	Minor

Conditions
1. The alteration does not result from unexpected events that occurred in manufacturing. 2. The alteration is within the approved range. 3. There is no alteration in method, or alterations in method are minor. 4. The proposed method does not involve a new, not yet standardized, technique or a standardized technique used alternatively. 5. The new method is not biological (pharmacopoeial microbiological methods are excluded). 6. The alteration is not related to mutagenic or elemental impurity. Any new impurity must be controlled with an appropriate acceptance criterion. 7. The specification parameter is not related to any critical parameters, such as content, impurities (except for solvent not used in the API manufacture); any physical characteristics (particle size, density or beat density, identification, water). 8. There is no alteration in the API synthesis route.
Documents
1. Comparative table between approved and proposed specifications. 2. Description of new analytical methods and validation data, if relevant. 3. Analysis of two API production batches with all specification parameters. 4. Justification/ risk assessment by the DIFA holder demonstrating that the test is not significant.

5. Justification/ risk assessment by the DIFA holder demonstrating that the excluded or expanded parameter is in accordance with the principles and acceptance criteria of ICH M7 Guide. 6. Discussion of risk analysis and summary for elementary impurities. 7. If new sites are involved, list (with full corporate name and address) of all approved and proposed sites. Statements that the API manufacture is carried out in accordance with the DIFA and the good manufacturing practices, and that the proposed site is available to be inspected (Article 9, item I). 8. Statement by the DIFA holder that there is no alteration in the synthesis route/ manufacturing process (or, in the case of API obtained from plant raw material, where appropriate, geographical origin and production), quality control procedures, and API specification (with the exception of the particle size distribution).

2.8 Alteration in API analytical method	Conditions	Documents	Type of amendment
1. Minor alteration in the API analytical method.	1, 2, 3, 4	1, 2	Immediate notification
2. Alteration of biological method, including replacement or inclusion.		1, 2	Minor
3. Method alteration resulting from compendium update.	5	3	Annual notification

Conditions
1. Validation studies must be carried out and demonstrate that the new method is at least equivalent to the approved one. 2. There is no alteration in total impurities' acceptance criterion; there are no new non-qualified impurities detected. 3. There is no alteration in the method (e.g. alteration in the length or temperature of the column, but not in the column type). 4. The new method is not biological (pharmacopoeial microbiological methods are excluded). 5. The alteration results from the update of an already adopted compendium.
Documents
1. Description of the revised analytical method and specification. 2. Comparative validation results or, if justifiable, comparative analysis results

demonstrating that the new method is at least equivalent to the approved one. 3. Complementary studies, if applicable.

2.9 Alteration in API primary packaging	Conditions	Documents	Type of amendment
1. Composition.	1, 2, 3	1, 2, 3	Immediate notification
2. Composition for sterile API.			Major (*)
3. Composition for liquid (non-sterile) API.		1, 2, 4, 5	Minor

Conditions
1. The proposed packaging material must be at least equivalent to the approved one in relation to the relevant properties. 2. Stability studies initiated of, at least, two pilot scale batches. 3. API is not sterile or liquid.
Documents
1. Comparison between the specification of the approved and proposed primary packaging material, if applicable. 2. Appropriate data regarding the proposed packaging material, including confirmation that it complies with the requirements for packaging and materials that come into contact with food. 3. Statement by the DIFA holder that stability studies were initiated (including the number of batches) and that minimum stability data were available, and that the results were satisfactory at the time of implementation. It must also be stated that the studies will be finalized, and that out-of-specification results will be notified to Anvisa, accompanied by an action plan. 4. Where applicable, data must be provided that there is no interaction between the API and the packaging material (e.g. leaching of impurities from the packaging material to the API or sorption of the contents by the packaging material), including information that the packaging material meets compendial requirements or the applicable food legislation. 5. Stability reports of, at least, two batches of, at least, pilot scale. It must include a statement that the studies will be finalized, and that out-of-specification results shall be notified to Anvisa, accompanied by an action plan. *The documentation must include a stability report comparative between the

approved and the proposed conditions of, at least, two batches of, at least, pilot scale.

2.10 Alteration in the API primary packaging specification parameters and/ or acceptance criteria	Conditions	Documents	Type of amendment
	1, 2, 3	1	Annual notification
Conditions			
1. The alteration does not result from unexpected events occurring in the packaging material manufacturing process or during API storage. 2. There is no alteration in method, or method alterations are minor. 3. Any new method does not involve non-standard methodology or standard methodology used alternatively.			
Documents			
1. Comparative table between the approved and the proposed specifications.			

2.11 Alteration in the composition or specification of the secondary packaging of the API	Conditions	Documents	Type of amendment
1. Composition.		1	Immediate notification
2. Specification.	1	1	Annual notification
Conditions			
1. The composition of the secondary packaging material of the API remains the same.			
Documents			
1. Comparison between the approved and the proposed specification or composition.			

2.12 Alteration in the API retest period or conservation care	Conditions	Documents	Type of amendment
1. Reduction in the approved retest period.	1	1	Immediate notification
2. Extension of the API retest period and/ or alteration in API conservation care.		2	Minor
3. Restriction of conservation care.	1	1	Immediate notification
4. Alteration in the approved stability protocol.	1, 2	3	Immediate notification
Conditions			

1. The alteration does not result from unexpected events that occurred in the manufacturing process. 2. The alteration does not represent an expansion of acceptance criteria in the tested parameters, removal of parameters indicative of stability and reduction of the frequency of tests.
Documents
1. Justification for removal of or reduction in the retest period, or for the adoption of more restrictive conservation care. 2. Updated data from stability studies of at least two pilot or industrial scale batches. 3. Justification for the proposed alterations.

2.13 Introduction of a new design space or application of a design space for the API, related to:	Conditions	Documents	Type of amendment
1. A unitary operation of the API process, including in-process controls and/ or tests or methods.		1, 2, 3	Major
2. Tests or methods for starting materials, reagents, intermediates, or API.		1, 2, 3	Major
Documents			
1. The design space was developed according to ICH Guides. Results of process, product, and analytical development studies (e.g. interaction of different parameters that integrate the design space) must be investigated, including risk analysis and multivariate studies, as appropriate. The investigation must show, where relevant, a systematic mechanistic understanding of material attributes and process parameters with the critical quality attributes of the API. 2. Description of the design space in table format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges. 3. Update of the relevant CTD Sections.			

2.14 Inclusion of the alteration management protocol related to the API	Conditions	Documents	Type of amendment
		1, 2, 3	Major
Documents			
1. Detailed justification of the proposed alteration. 2. Alteration management protocol related to the API.			

3. Update of the relevant CTD Sections.

2.15 Exclusion of an alteration management protocol related to the API	Conditions	Documents	Type of amendment
	1	1, 2	Immediate notification

Conditions
1. The exclusion of the API alteration management protocol does not result from unexpected events occurring in the manufacturing process or out-of-specification results that occurred during the implementation of the alteration described in the protocol, and does not imply alterations to information already approved in the dossier.
Documents
1. Justification of the proposed exclusion. 2. Update of the relevant CTD Sections.

2.16 Amendment of an alteration management protocol	Conditions	Documents	Type of amendment
1. Major amendments to the alteration management protocol.			Major
2. Minor amendments to the alteration management protocol that do not affect the control strategy defined in the protocol.		1	Minor

Documents
1. Statement that any alterations are within the range of the currently approved acceptance criteria.

2.17 Implementation of alterations provided for in the alteration management protocol approved	Conditions	Documents	Type of amendment
1. The implementation does not require additional evidence.	1	1, 2, 3	Immediate notification
2. The implementation requires additional evidence.		1, 2, 3, 4	Minor

Conditions
1. The proposed alteration was carried out in accordance with the alteration management protocol approved.
Documents
1. Reference to the alteration management protocol approved. 2. Statement that the alteration is in accordance with the alteration management protocol approved and that the results of

the study reveal that the acceptance criteria provided for in the protocol have been met. 3. Update of the relevant CTD Sections. 4. Results of studies conducted according to the alteration management protocol approved.

ANNEX III – CLASSIFICATION OF DIFA TECHNICAL DOCUMENTS IN OPEN PART AND RESTRICTED PART

	Open part	Restricted part	Correspondence with CTD Guide
Section I – General Information	x		3.2.S.1
Subsection I – Nomenclature	x		3.2.S.1.1
Subsection II – Structure	x		3.2.S.1.2
Subsection III – General Properties	x		3.2.S.1.3
Section II – Manufacturing	x	x	3.2.S.2
Subsection I – Manufacturer(s)	x		3.2.S.2.1
Subsection II – Description of the API Manufacturing Process and In-Process Controls	(a)	(b)	3.2.S.2.2
Subsection III – Control of Raw Materials		x	3.2.S.2.3
Subsection IV – Control of Critical Steps and Intermediates	(c)	(d)	3.2.S.2.4
Subsection V – Process Validation	(e)	x	3.2.S.2.5
Subsection VI – Manufacturing Process Development		x	3.2.S.2.6
Section III – Characterization	x		3.2.S.3
Subsection I – Elucidation of Structure and Other Characteristics	x		3.2.S.3.1
Subsection II – Impurities	x	(f)	3.2.S.3.2
Section IV – Quality Control	x		3.2.S.4
Subsection I – Specification	x		3.2.S.4.1
Subsection II – Analytical Methods	x		3.2.S.4.2
Subsection III – Validation of analytical methods	x		3.2.S.4.3
Subsection IV – Batch Analysis	x		3.2.S.4.4
Subsection V – Specification Justification	x	(g)	3.2.S.4.5
Section V – Reference Materials and Chemical Substances	x		3.2.S.5
Section VI – Packaging	x		3.2.S.6
Section VII – Stability	x		3.2.S.7
Subsection I – Stability Summary	x		3.2.S.7.1
Subsection II – Post-submission Protocols and Commitments	x		3.2.S.7.2
Subsection III – Stability data and reports	x		3.2.S.7.3

(a) The open part must contain at least a diagram of the synthesis route and a simplified description of the manufacturing process, from the introduction of the starting material.

(b) The restricted part must contain all information relevant to the manufacturing process.

(c) Information that is also relevant for the medicinal product marketing authorization petitioner.

(d) Information related to the detailed description of the manufacturing process and not relevant for the medicinal product marketing authorization petitioner.

(e) For sterile API, when there is no additional sterilization step in the medicinal product manufacturing process.

(f) Information on potential impurities that refers to the sequential narrative of the manufacturing process may appear in the restricted part, provided that there is unequivocal proof that they do not need to be controlled in the API.

(g) Information regarding the sequential narrative of the manufacturing process, raw material control, and process validation may appear in the restricted part.