RESOLUTION OF THE BOARD OF DIRECTORS - RDC nº 359/2020

TITLE I

PRELIMINARY PROVISIONS

Art. 1º This Resolution institutes the Active Pharmaceutial Ingredient Dossier (DIFA) and the Letter of Suitability of the Active Pharmaceutical Ingredient (CADIFA).

CHAPTER I

SCOPE

Art. 2º This Resolution applies to active pharmaceutical ingredients (API) used in the manufacture of new, innovator, generic and similar drug products.

§ 1º This Resolution does not apply to APIs used in the formulation of notified pharmaceutical products, biological products, herbal drug preparations and drug products classified as specific, homeopathic, antihomotoxic and anthroposophic.

§ 2º This Resolution does not apply, in addition, to APIs listed in § 1º used in fixed dose combination with synthetic or semisynthetic APIs in drug products classified as new, innovator, generic or similar.

CHAPTER II

DEFINITIONS

Art. 3º In the context of this Resolution, the following definitions are adopted:

I - Letter of Suitability of the Active Pharmaceutical Ingredient (CADIFA): administrative instrument that attests the compliance of the API with the requirements of this Resolution.;

II - CADIFA holder: DIFA holder, after the granting of the CADIFA;

III - DIFA holder: company that possesses the knowledge about the entire manufacturing process of the API and under whose oversight the manufacture of the API is conducted, from the introduction of the starting material;

IV - Active Pharmaceutical Ingredient Dossier (DIFA): collection of administrative and technical documents of an active pharmaceutical ingredient;

V - active pharmaceutical ingredient (API): any substance used in the formulation of a dosage form that, when administered to a patient, acts as an active ingredient. Such substances are intended to exert pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

VI - expression of interest: procedure through which the DIFA holder states its interest in applying for a CADIFA through a standalone CADIFA application (i.e., not associated with a drug product marketing authorization or variation);

VII - new chemical entity: API used in the formulation of a new drug product.

Single clause. In addition, the definitions of ICH guidelines referenced in this Resolution as well as those from other ANVISA Resolutions are adopted.

TITLE II

ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA) AND LETTER OF SUITABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENT (CADIFA)

CHAPTER I

SUBMISSION OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Art. 4º The Active Pharmaceutical Ingredient Dossier (DIFA) as well as changes to the DIFA should be submitted to ANVISA by its holder.

Single clause. ANVISA may, at its discretion, request the submission of the DIFA in the following circumstances:

I - after an expression of interest submitted by the DIFA holder; or

II - after an invitation by the Board of Directors.

Art. 5º After the submission of the DIFA according to art. 4º, a reference number will be generated.

CHAPTER II

ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Art. 6º The DIFA should contain a version number and table of contents. Its documents should be organized in the order 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.

Art. 7º The assessment of the Active Pharmaceutical Ingredient Dossier (DIFA) and its changes is comprised of the evaluation of administrative and quality documents.

Art. 8º Deficiency letters and communications of approval or rejection will be sent directly to the DIFA holder.

Single clause. If the DIFA or its changes are rejected, a reconsideration request may be submitted, according to RDC 266/2019.

CHAPTER III

ADMINISTRATIVE DOCUMENTS OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Art. 9º. The Active Pharmaceutical Ingredient Dossier (DIFA) should contain the following administrative documents:

I - filled in application form and declarations stating the responsibilities of the DIFA holder with ANVISA and with the marketing authorization applicant/holder; and

II - evaluation of the DIFA holder regarding the risk of transmission of spongiform encephalopathy or, when applicable, declaration that raw materials from human or animal origin are not used.

CHAPTER IV

QUALITY DOCUMENTS OF THE ACTIVE PHARMACEUTICAL INGREDIENT DOSSIER (DIFA)

Art. 10. The quality sections of the DIFA should be organized according to the quality module of the active pharmaceutical ingredient (3.2.S) of Guia 24/2019, Annex 2 (or ICH M4Q).

§ 1º When there are confidentiality restrictions between the DIFA holder and the marketing authorization applicant/holder, the quality documents should be divided into applicant's and restricted parts, according to Annex III of this Resolution.

§ 2º The applicant's part should contain sufficient information to allow the marketing authorization applicant/holder to evaluate the quality of the API and its suitability for the manufacture of the drug product.

Art. 11. The Active Pharmaceutical Ingredient Dossier (DIFA) should comply with the requirements for APIs of the following ICH guidelines and supplementary documents:

I - ICH Q1A - Stability Testing of New Drug Substances and Products;

II - ICH Q1B - Stability Testing: Photostability Testing of New Drug Substances and Products;

III - ICH Q1D - Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products;

IV - ICH Q1E - Evaluation for Stability Data;

V - ICH Q2(R1) - Validation of Analytical Procedures: Text and Methodology;

VI - ICH Q3A(R2) - Impurities in New Drug Substances;

VII - ICH Q3C(R6) - Impurities: Guideline for Residual Solvents;

VIII - ICH Q3D(R1) - Guideline for Elemental Impurities, according to ANNEX I of this Resolution;

IX - ICH Q6A - Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances;

X - ICH Q11 - Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities); and

XI - ICH M7(R1) - Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk;.

Art. 12. ANVISA may request studies and documents not listed in this Resolution, provided that the request is justified by issues related to the safety and quality of the API and in accordance with international guidelines.

Art. 13. Alternative approaches to this Resolution should be justified and supported by a technical/scientific rationale .

Section I

General Information (3.2.S.1)

Subsection I

Nomenclature (3.2.S.1.1)

Art. 14. The Brazilian Nonproprietary Name (DCB) or International Nonproprietary Name (INN), chemical name, CAS registry number, compendial name and, if relevant, other names should be provided.

Subsection II

Structure (3.2.S.1.2)

Art. 15. The structural formula, including stereochemical configuration, molecular formula and relative molecular mass should be provided.

Subsection III

General Properties (3.2.S.1.3)

Art. 16. A list of physicochemical properties and other relevant properties should be provided, in particular those that affect the efficacy and safety of the drug product, such as solubility, pKa, polymorphism, isomerism, partition coefficient (logP), permeability and hygroscopicity.

Section II

Manufacture (3.2.S.2)

Subsection I

Manufacturer(s) (3.2.S.2.1)

Art. 17. The name, address and responsibility of the units that perform manufacturing steps of intermediates and API and quality control of the API, from the introduction of the starting material(s), should be provided.

Single clause. When physical steps (e.g., milling, micronization, lyophilization) or sterilization are performed by the DIFA holder of under its oversight, the unit(s) should be included, as well as contractors.

Subsection II

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

Art. 18. The synthetic scheme, from the introduction of the starting material(s), should be provided.

§ 1º The molecular formula, relative molecular mass and structural formula, including stereochemical configuration, of starting materials, intermediates and the API should be indicated .

§ 2º Non-isolated intermediates should be depicted between brackets.

§ 3º Solvents, reagents, catalysts and other raw materials used in the manufacturing process should be described and the steps at which they are used should be indicated.

Art. 19. A sequential procedural narrative should be provided, including:

I - Process parameters, including quantities or ranges of raw materials, starting materials, intermediates, solvents, catalysts and reagents used in the manufacture of industrial-scale batches, as well as operating conditions (e.g., temperature, pressure, pH, time, flux, etc.), should be provided;

II - identification of critical steps and process controls; and

III - scale of manufacture and yield ranges for each manufacturing step.

Art. 20. A flow chart of the manufacturing process, containing the sequence of unit operations and indication of input and output of materials and process controls, should be provided.

Art. 21. If routine reprocessing is performed, the procedure and circumstances in which it is employed should be described.

Art. 22. If solvents or other recovered materials are used, the maximum ratio and steps from which the solvent/material is recovered and reintroduced should be informed.

Art. 23. Alternative processes with substantially differente synthetic routes should constitute separate DIFAs, even if the specifications and impurity profile of downstream intermediates and the API are the same.

Art. 24. If recycled mother liquors are employed, the information should be described in the sequential procedural narrative.

Art. 25. Reworking procedures shoud not be included in the DIFA.

Art. 26. For sterile APIs, the description of the sterilization process should be provided.

Art. 27. For APIs obtained through fermentation or in which the substance isolated from the fermentation process or a downstream intermediate does not meet the criteria for selection of starting materials for synthetic APIs, the following additional information should be provided:

I - description of the manufacturing process;

II - source and type of microorganism;

III - procedures and controls for preparation of master and working cell banks;

IV - composition of media;

V - control of microbial bioburden in the fermentation process;

VI - precursors or metabolic substrates if applicable;

VII - process parameters (time, temperature, rate of aeration, etc.);

VIII - name and composition of preservatives;

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

Art. 28. For APIs derived from botanical materials in which the substance isolated from the botanical material or a subsequent intermediate does not meet the criteria for selection of starting materials for synthetic APIs, the following additional information should be provided:

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

II - geographical origin;;

III - time of harvest, if relevant;

IV - information on the use of chemical fertilizers, pestices, fungicides, etc.;

V - potential sources of contamination; and

VI - process controls and operating conditions.

Subsection III

Control of Materials (3.2.S.2.3)

Art. 29. A list of raw materials used in the manufacturing process should be provided.

Single clause. All materials used in the manufacturing process are classified as raw materials, including starting materials, reagents, solvents, catalysts, substrates, auxiliary materials and recovered materials.

Art. 30. The specification and analytical methods for all raw materials should be provided, as well as batch analysis, when relevant.

§ 1º The quality of raw materials should be appropriate for their intended use.

§ 2º The specification of recovered solvents and recovered materials should be justified.

§ 3º If the specification of a recovered material contains wider acceptance criteria than those of the fresh grade, the DIFA holder should demonstrate that the quality of the API manufactured with the recovered material is equivalent to that of the API manufactured with the fresh grade.

Art. 31. For starting materials, the following information should be provided:

I - name and chemical structure;

II - specification;

III - analytical methods;

IV - name and address of manufacturers;

V - synthetic route for each manufacturer, including reagents, solvents and catalysts;

VI - batch analysis; and

VII - justification for selection of the starting material.

§ 1º The specification of the starting materials should be justified and should include, as applicable, tests for specified and unspecified impurities, total impurities, solvents, catalysts, elemental impurities and mutagenic impurities.

§ 2º For semisynthetic APIs whose starting material is obtained by fermentation or derived from a substance obtained by fermentation, the justification for selection of the starting material should include a discussion on the carry-over of impurities arising from the fermentation process (ex. DNA, proteins) into the API.

§ 3º For semi-synthetic APIs whose starting material is isolated from a botanical material or derived from a substance isolated from a botanical material, the justification for selection of the starting material should include a discussion on the carry-over of impurities arising from cultivation (ex. pesticides, heavy metals, aflatoxins) and the extraction process into the API.

§ 4° When there is more than one manufacturer of a starting material, a discussion regarding the specification of the starting material with respect to the differences in the manufacturing processs of different sources should be provided.

§ 5º A technically inadequate justification of the starting material will lead to a redefinition request.

Subsection IV

Controls of Critical Steps and Intermediates (3.2.S.2.4)

Art. 32. Tests and acceptance criteria, with justification including experimental data, performed at critical steps identified in the sequential procedural narrative should be provided.

Art. 33. The specification and analytical methods of isolated intermediates should be provided.

Single clause. The specification of intermediates should be justified and should include, as applicable, tests for specified and unspecified impurities, total impurities, solvents, catalysts, elemental impurities and mutagenic impurities.

Art. 34. For non-isolated intermediates, tests and parameters used to determine reaction end-points should be provided or their absence justified.

Subsection V

Process Validation (3.2.S.2.5)

Art. 35. The manufacturing process of the API, from the starting material, should be validated prior to marketing.

Art. 36. For sterile APIs, the following information should be provided:

I - justification for the sterilization method; and

II - validation studies, protocols and reports for sterilization and aseptic processing steps.

Subsection VI

Manufacturing Process Development (3.2.S.2.6)

Art. 37. For new chemical entities, a description and discussion regarding significant changes made to the manufacturing process or manufacturing site of the API should be provided, including:

I - non-clinical batches;;

II - clinical batches;

III - scale-up batches;

IV - pilot batches; and

V - commercial scale batches, if available.

Single clause. For APIs not classified as new chemical entities, the DIFA holder may include data from the manufacturing process development to support the control strategy.

Art. 38. For APIs developed by quality by design, the studies that support the design space should be provided.

Single clause. For APIs developed by quality by design, the DIFA holder should comply with ICH Q8(R2) (Pharmaceutical Development), Q9 (Quality Risk Management) e Q10 (Pharmaceutical Quality System).

Section III

Characterization (3.2.S.3)

Subsection I

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

Art. 39. Elucidation of the chemical structure should be provided, based on the synthetic route and appropriate instrumental methods.

Single clause. For APIs for which a pharmacopoeial reference standard is available, comparative identification tests may be provided.

Art. 40. A discussion and characterization of solid phase properties of the API should be provided, as applicable.

Subsection II

Impurities (3.2.S.3.2)

Art. 41. A detailed discussion regarding all potential impurities should be provided, incluing reagents, catalysts, by-products, solvents and degradation products. The discussion should comprise:

I - formation, fate and purge; and

II - control strategy and proposed acceptance criteria.

§ 1º The discussion should comprise specified and unspecified impurities, total impurities, elemental impurities, mutagenic impurities and justification for the absence of tests for potential impurities that are not controlled.

§ 2º Based on risk assessment, the validation of critical parameters of analytical procedures used in carry-over studies should be provided.

Section IV

Control of the API (3.2.S.4)

Subsection I

Specification (3.2.S.4.1)

Art. 42. The specification of the API should be provided, including tests, references to analytical procedures and acceptance criteria to which the API should comply to be considered acceptable for its intended use.

Subsection II

Analytical Procedures (3.2.S.4.2)

Art. 43. Analytical procedures used for release and stability studies should be provided.

Subsection III

Validation of Analytical Procedures (3.2.S.4.3)

Art. 44. Validation of analytical procedures used for release and stability studies should be provided, according to RDC 166/2017 or ICH Q2 (Validation of Analytical Procedures).

Subsection IV

Batch Analyses (3.2.S.4.4)

Art. 45. Batch results for at least three batches manufactured according to the proposed manufacturing process and specification should be provided.

Single clause. Batch analysis to support significant variables of the manufacturing process should be provided, according to Annex II of this Resolution.

Art. 46. For new chemical entities, batch analysis of batches referenced in art. 37 should be provided.

Art. 47. Batch analysis should contain, at least, the following information:

I - date of manufacture;

II - size and batch number;

III - site of manufacture; and

IV - results for all tests listed in the specification.

Single clause. The absence of tests that are listed in the specification or unexpected results should be justified.

Subsection V

Justification of Specification (3.2.S.4.5)

Art. 48. A justification for the API specification should be provided.

Art. 49. The justification of the API specification should be based, as applicable, on:

I - non-clinical and clinical studies;

II - impurity qualification studies;

III - batch results;

IV - monographs of officially recognized compendia by ANVISA, according to RDC 37/2009;

V - in-process controls, control of intermediates and critical steps;

VI - carry-over studies for impurities; and

VII - ICH guidelines listed on art. 11 of this Resolution.

Section V

Reference Standards or Materials (3.2.S.5)

Art. 50. Information on reference and working standards should be provided.

Section VI

Container Closure System (3.2.S.6)

Art. 51. The description and specification of packaging materials should be provided.

§ 1º For functional secondary packaging materials, information relevant to the function should be provided.

§ 2º For non-functional secondary packaging materials, a brief description should be provided.

§ 3º The specification of primary packaging materials should contain identification and description tests.

Art. 52. A discussion regarding the following attributes should be provided, as applicable:

I - protection from light;

II - protection from moisture;

III - compatibility between the primary packaging material and the API, including the possibility of sorption to container or leaching of impurities that might compromise the API quality; and

IV - compliance with requirements for food grade materials.

Section VII

Stability (3.2.S.7)

Subsection I

Stability Summary (3.2.S.7.1)

Art. 53. A summary of the stability protocol, stability studies and results should be provided, according to RDC 318/2019.

Single clause. The proposed storage conditions and retest period or shelf life should be stated.

Subsection II

Post-approval Stability Protocol and Stability Commitment (3.2.S.7.2)

Art. 54. A post-approval stability protocol and stability commitment should be provided, according to RDC 318/2019.

Art. 55. If the proposed retest period or shelf life is based on extrapolation, a commitment to continue the stability studies until the appropriate time-point should be provided.

Subsection III

Stability Data and Reports (3.2.S.7.3)

Art. 56. The stability results should be provided, according to RDC 318/2019.

CHAPTER V

LIFE CYCLE OF THE API

Art. 57. The DIFA holder should submit the changes to the DIFA to ANVISA, according to the conditions and supporting documentation of ANNEX II of this Resolution.

§ 1º The changes to the DIFA are classified as:

I - annual notification;

II - immediate notification;

III - minor; or

IV - major.

§ 2º Changes not described in ANNEX II should be classified as minor..

§ 3º For changes for which the column “documents” is blank or changes referenced in § 2º, the supporting documentation should be compatible with the nature and complexity of the change, considering:

I - DIFA sections directly affected by the change; and

II - DIFA sections in which additional studies should be included to support the change.

Art. 58. If a change is approved, ANVISA will issue a revised CADIFA in the following cases:

I - Notification or minor change that alter the content of the CADIFA; or

II - Major change, regardless of whether it alters the content of the CADIFA.

Art. 59. The DIFA holder should inform the marketing authorization applicant/holder of changes that are subject or not to regulatory approval, when required by good manufacturing practices or quality agreements.

Section I

Submission of Changes

Art. 60. For each change, the DIFA holder should submit to ANVISA the:

I - application form; and

II - supporting documentation.

Art. 61. Changes that are associated with or arise from other changes should be submitted in a single application and classified according to stricter reporting category among the changes.

Section II

Classification of Changes

Art. 62. Annual and immediate notification changes do not require prior communication to ANVISA for implementation.

Art. 63. Annual notification changes should be submitted within 12 months of implementation.

Art. 64. Immediate notification changes should be submitted immediately after implementation.

Art. 65. Minor and major changes require approval from ANVISA for implementation.

Single clause. If ANVISA does not issue a communication within 60 (sixty) days of receipt of the documentation, for minor changes, or 180 (one hundred and eighty) days, for major changes, the change can be implemented.

Art. 66. The implementation of the change does prevent its assessment, at any time, at which point ANVISA can request additional information, approve or reject the change.

Single clause. If a change is rejected, the approved condition prior to the change should be immediately reestablished after the communication by ANVISA.

CHAPTER VI

LETTER OF SUITABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENT (CADIFA)

Art. 67. If the DIFA is approved, ANVISA will issue a Letter of Suitability of the Active Pharmaceutical Ingredient (CADIFA) to the DIFA holder.

Single clause. When issued according to single clause of art. 4º, the name and address of the DIFA holder, DIFA version number e CADIFA number will be published on ANVISA's website.

Art. 68. The following information will be included in the CADIFA:

I - number and issue date of the CADIFA;

II - Brazilian nonproprietary name (DCB), DCB number and CAS registry number;

III - name and address of DIFA holder;

IV - name and address of manufacturing sites;

V - API specification and, if applicable, compendial reference;

VI - container closure system;

VII - storage conditions of the API;

VIII - retest period or shelf life; and

IX - field for declaration of access.

§ 1º Additional information considered relevant may be included in the CADIFA.

§ 2º Item IV comprises:

I - manufacturing sites of the API and intermediates; and

II - sterilization sites and sites that perform physical steps (e.g., micronization, milling, sieving, lyophilization), when these steps are conducted under the oversight of the DIFA holder.

Art. 69. Manufacturing sites must comply with good manufacturing practices for APIs.

Single clause. The CADIFA will not be issued if non-compliance with good manufacturing practices is evidenced.

CHAPTER VII

SUSPENSION AND WITHDRAWAL OF THE LETTER OF SUITABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENT (CADIFA)

Art. 70. The suspension and withdrawal of the CADIFA will be communicated to the DIFA holder and marketing authorizations holders to which the CADIFA is associated.

Single clause. When the CADIFA is issued according to single clause of art. 4º, the suspension and withdrawal of the CADIFA will be published on ANVISA's website.

Section I

Suspension of the CADIFA

Art. 71. The following circumstances may lead to the suspension of the CADIFA:

I - inspection conducted by the National System of Health Surveillance (SNVS) or by organizations with which ANVISA has cooperation agreements that shows critical and/or major deficiencies that lead to the conclusion that the manufacturing process of the API does not comply with GMP, posing a public health risk;

II - evidence that the API is not manufactured according to the DIFA;

III - failure to reestablish the previously approved conditions, in the case of rejection of changes implemented with no prior approval from ANVISA;

IV - failure to conduct technical changes to which the DIFA holder committed prior to the CADIFA issuance or due to mandatory updates; or

V - refusal to be inspected.

§ 1º The CADIFA will be restored if compliance with current regulations, deficiency letters or other requests issued by ANVISA or, when applicable, by organizations with which ANVISA has cooperations agreements is demonstrated.

§ 2º ANVISA may suspend the CADIFA for reasons not mentioned in this Resolution, as an adequately justified preventive measure, with the objective of avoiding exposure of the population to health risks.

Art. 72. The CADIFA holder may request its suspension if unable to comply with regulatory requirements.

§ 1º The suspension is limited to a period of 2 (two) years, except if a justification is provided and accepted by ANVISA.

§ 2º The restoration of a CADIFA must requested by its holder.

Art. 73. The suspension of a CADIFA may lead to suspension of importation for imported APIs or suspension of manufacture or marketing for APIs manufactured in Brazil.

Art. 74. The suspension of a CADIFA may lead to the suspension of importation, manufacture or marketing of drug products whose marketing authorization are associated with the CADIFA.

Section II

Withdrawal of the CADIFA

Art. 75. A CADIFA poderá ser cancelada em decorrência de:

I - inspection conducted by the National System of Health Surveillance (SNVS) or by organizations with which ANVISA has cooperation agreements that shows critical and/or major deficiencies that lead to the conclusion that the manufacturing process of the API does not comply with GMP, posing a severe public health risk.;

II - conclusion that the API is not manufactured according to the DIFA, posing severe public health risks;

III - submission of falsified information in the initial submission of API lifecycle;

IV - recurrence in issues that lead to the suspensaion of a CADIFA;

V - failure to comply with ANVISA's requests after the suspension of a CADIFA;

VI - cessation of production or closure of the site; or

VII - two-year period elapsed for a suspended CADIFA, except in the case of § 1º of art. 72.

Single clause. ANVISA may withdraw the CADIFA for reasons not mentioned in this Resolution, as an adequately justified preventive measure, with the objective of avoiding exposure of the population to severe public health risks.

Art. 76. The CADIFA holder may request its withdrawal.

Art. 77. The CADIFA withdrawal, when due to public health risks, will lead to the suspension of importation for imported APIs or suspension of manufacture or marketing for APIs manufactured in Brazil.

Art. 78. The CADIFA withdrawal may lead to the suspension of importation, manufacture or marketing of the drug product whose marketing authorization is associated with the CADIFA.

TITLE III

FINAL AND TRANSITORY PROVISIONS

Art. 79. The manufacturers of APIs listed below that have not been regularized according to Resolution RDC nº 57/2009 are excluded from the drug product marketing authorizations in which they are listed as approved.

§ 1° Art. 79 applies to:

I - aciclovir;

II - aciclovir sodium;

III - ampicillin;

IV - ampicillin benzathine;

V - ampicillin potassium;

VI - ampicillin sodium;

VII - ampicillin trihydrate;

VIII - azithromycin;

IX - azithromycin dihydrate

X - azithromycin monohydrate;

XI - benzylpenicillin;

XII - benzylpenicillin benzathine;

XIII - benzylpenicillin potassium;

XIV - benzylpenicillin procaine;

XV - benzylpenicillin sodium;

XVI - cabergoline;

XVII - carbamazepine;

XVIII - lithium carbonate

XIX - carboplatin;

XX - cefalexin

XXI - cefalexin monohydrate;

XXII - cefalexin sodium;

XXIII - cefalotin;

XXIV - cefalotin sodium;

XXV - ceftazidime;

XXVI - ceftazidime pentahydrate;

XXVII - ceftazidime sodium;

XXVIII - ceftriaxone;

XXIX - ceftriaxone disodium hemipentahydrate;

XXX - ceftriaxone sodium;

XXXI - cyclophosphamide;

XXXII - cyclophosphamide monohydrate;

XXXIII - ciclosporin;

XXXIV - ciprofloxacin;

XXXV - cisplatin;

XXXVI - clarithromycin;

XXXVII - clindamycin;

XXXVIII - cephalexin hydrochloride;

XXXIX - ciprofloxacin hydrochloride;

XL - ciprofloxacin hydrochloride monohydrate;

XLI - clindamycin hydrochloride;

XLII - clindamycin hydrochloride monohydrate;

XLIII - penicillamine hydrochloride;

XLIV - tiabendazole hydrochloride;;

XLV - valacyclovir hydrochloride;

XLVI - clindamycin palmitate hydrochloride

XLVII - clozapine;

XLVIII - efavirenz;

XLIX - phenytoin;

L - phenytoin sodium;

LI - clindamycin phosphate;

LII - thiabendazole hypophosphite;

LIII - ciprofloxacin lactate;

LIV - clarithromycin lactobionate;

LV - lamivudine;

LVI - cefalexin lysinate;

LVII - methotrexate;

LVIII - methotrexate sodium;

LIX - nevirapine;

LX - nevirapine hemihydrate;

LXI - penicillamine;

LXII - rifampicin;

LXIII - ritonavir;

LXIV - sultamicillin;

LXV - thiabendazole;

LXVI - sultamicillin tosylate;

LXVII - valaciclovir; and

LXVIII - zidovudine

§ 2º The manufacture of drug products whose marketing authorization does not have any remaining approved API manufacturers is suspended until a new API manufacturer is included.

Art. 80. Non-compliance with the requirements of this Resolution constitutes an infraction under Law nº 6.437/1977, not excluding penal, civil and administrative liability.

Art. 81. On March 1st, 2021, the following normatives are revoked:

I - Resolução de Diretoria Colegiada - RDC nº 57/2009, from November 17, 2009;

II - Instrução Normativa nº 15, from November 17, 2009;

III - Instrução Normativa nº 3, from June 28, 2013;

IV - Nota Técnica Conjunta 01/2016 - COIFA/GGMED - COINS/GIMED, from April 22, 2016; and

V - Nota Técnica nº 06-001/2015- COISC/GGINP/SUINP/ANVISA - COIFA/GGMED/SUMED/ANVISA.

Art. 82 This Resolution will take effect on August 3, 2020.

ANNEX I

IMPLEMENTATION OF ICH Q3D BY DIFA HOLDER

Regardless of this annex, specific tests for elemental impurities that are listed in the monograph should be part of the API specification, except if their absence is adequately justified.

For DIFAs submitted according to single clause of art. 4º, there will not be a final conclusion regarding the acceptability of the proposed acceptance criteria. This assessment will be conducted in the context of the marketing authorization application/variation.

When the risk assessment for elemental impurities of the API is integrated with that of the drug product, the DIFA holder does not have to provide additional information regarding elemental impurities. In the remaining cases, the DIFA holder should follow one of the following strategies (1 or 2):

1 Risk Management Summary provided (RMS):

DIFA holders should state this option in their application.

The RMS report should be preferably included in ''Subsection II - Impurities (3.2.S.3.2)"" and it should detail the rationale used to conduct the study, as well as a justification of the control strategy implemented following the risk assessment. When there are confidentility restrictions, the RMS table should be included in the applicant's part.

If insufficient data is provided, the application will be considered as if no RMS is provided.

1.1 Requirements

In addition to ICH Q3D principles, the DIFA holder should consider the following instructions when opting for a RMS strategy:

a) How to conduct the RMS:

The RMS should consider all potential sources of contamination, including elemental impurities intentionally introduced into the process after the introduction of the starting material, contributions from materials (such as contaminants in starting materials, reagents, water), equipment, and packaging..

The intended route of administration/use of the substance should be indicated, which forms the basis of the risk management discussion.

The RMS should consider all 24 elemental impurities mentioned in ICH Q3D Table 5.1, as follows:

- Class 1 and 2A elements, as well as all elements intentionally added in the manufacture whatever their classification should be systematically discussed.

- If relevant, and depending of the use of the substance, Class 3 elements should be discussed.

- Justification as to why specific elemental impurities were included in the scope of the RMS is considered useful information and should be included.

b) How to define the control strategy:

The control strategy should focus on the absence or presence of elemental impurities in the API relying on the process capabilities and on the control of elemental impurities, using preferably option 1, or alternatively, an acceptance criterion derived from the permitted daily exposure and maximum daily dose.

Absence of an elemental impurity can be concluded when it is shown with convincing evidence that it is purged to a level which is consistently below 30% of the acceptable acceptanche criterion, in a minimum of 3 consecutive commercial batches or a minimum of 6 consecutive pilot batches of the API.

When applicable, a justified specification for elemental impurities in the API should be introduced. For any elemental impurity intentionally introduced into the last synthetic step of the process, a specification in the API is expected (as this is associated with an elevated risk for impurities being carried forward), unless it is consistently and convincingly demonstrated that the process is capable to purge the impurity from the API to a level which is below 30% of the acceptable acceptance criterion.

Screening results of several batches for elemental impurities may support but do not replace a RMS. This might be done in a similar manner as is illustrated in appendix 4 of the ICH Q3D guideline.

With respect to analytical procedures:

For screening purposes, the analytical methodology used should be mentioned along with minimum validation information such as indication of the specificity and sensitivity of the method (LOD/LOQ).

For test included in the API specification, a detailed description of the analytical method used should be provided. The analytical method should be validated in accordance with the requirements of “Subsection III - Validation of Analytical Procedures” of this Resolution.

c) RMS Table

The following table, containing the RMS conclusion, should be included in the RMS.

This table is intended to provide necessary information about the level of contamination of the API source, in order to implement the ICH Q3D component approach in the drug product.

RMS Table				
Intended route of administration / Use of the API:				
Element	Class	Intentionally added?	Considered in risk management	Conclusion
Cd	1	*	Yes	**
Pb	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2a	*	Yes	**
V	2a	*	Yes	**
Ni	2a	*	Yes	**
Tl	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 explained under 1.1:
- “Absent” with its meaning definition (e.g. “less than 30% of ICH Q3D option 1 limit”, or “less than X ppm”),;
- or “< X ppm”;
- or “No risk identified”.

It is recommended not to include individual batch results in the table. The DIFA holder should ensure that the substance complies with the maximum level indicated.

2 No Risk Management Summary provided

2.1 Requirements

If no risk assessment has been performed, the following instructions should be followed:

- Any elemental impurities (whatever the Class) intentionally introduced in the manufacture of the API after the introduction of the starting material(s) should be declared and data showing their level in the API should be provided.

- For any elemental impurity intentionally introduced into the last synthetic step of the process, a specification in the API is expected (as this is associated with an elevated risk for impurities being carried forward), unless it is consistently and convincingly demonstrated that the process is capable to purge the impurity from the API to a level which is below 30% of the appropriate acceptance criterion (preferably option 1, or alternatively, an acceptance criterion derived from the permitted daily exposure and maximum daily dose).

- The acceptance criteria applied for the control of elemental impurities in the API should reflect the process capabilities, and the PDE of ICH Q3D may be used as reference.

- The analytical procedure used to control elemental impurities in the API should be described in detail and validation data according to the requirements of “Subsection III - Validation of Analytical Procedures (3.2.S.4.3)” should be provided.

ANNEX II

CHANGES, CONDITIONS AND SUPPORTING DOCUMENTATION OF THE DIFA

1 – Administrative Changes

1.1 Change in the name and/or address of the CADIFA holder	**Conditions**	**Documents**	**Type of change**
	1	1,2	Immediate notification
Conditions			
1. The CADIFA holder must remain the same legal entity (exception to this condition: where the company is sold or in the event of a company merger). Documents			
Documents			
1. A formal document from a relevant official body in which the new name and/or new address is mentioned.			
2. Updated declartions from item I of art. 9 of this Resolution.			

1.2 Change in the name and/or address of a manufacturing site or a quality control testing site for the API.	**Conditions**	**Documents**	**Type of change**
	1	1,2	Immediate notification
Conditions			
1. The location of the manufacturing site or the quality control site must remain the same.			
Documents			
1. A formal document from a relevant official body in which the new name and/or address is mentioned..			
2. Declarations that the manufacture of the API is conducted according to the DIFA and GMP and that the manufacturer is willing to be inspected (art. 9, item I).			

1.3 Change in the name and/or address of a manufacturer of a starting material used in the manufacture of the API.	**Conditions**	**Documents**	**Type of change**
	1	1	Annual notification
Conditions			
1. The location of the manufacturing site must remain the same.			
Documents			
1. Updated list (with name and complete address) of approved and proposed manufacturers of starting material.			

1.4 Change in the name and/or address of a manufacturer of an intermediate used in the manufacture of the API.	**Conditions**	**Documents**	**Type of change**
	1	1,2	Immediate notification
Conditions			
1. The location of the manufacturing site must remain the same.			
Documents			
1. Updated list (with name and complete address) of approved and proposed manufacturers of intermediate.			
2. Declarations that the manufacture of the API is conducted according to the DIFA and GMP and that the manufacturer is willing to be inspected (art. 9, item I).			

	Conditions	**Documents**	**Type of change**

1.5 Deletion of a manufacturer of intermediate or of a manufacturing site or quality control testing site for the API.	1	1,2	Immediate notification
Conditions			
1. There should at least remain one site/manufacturer, as previously declared, performing the same function as the one(s) concerned by the deletion.			
Documents			
1. The justification of the deletion.			
2. Updated list (with name and complete address) of approved and proposed sites.			

1.6 Deletion of a manufacturer of a starting material used in the manufacture of the final substance.	**Conditions**	**Documents**	**Type of change**
	1	1,2	Annual notification
Conditions			
1. There should at least remain one site, as previously declared, performing the function.			
Documents			
1. The justification of the deletion.			
2. Updated list (with name and complete address) of approved and proposed manufacturers of starting material.			

1.7 Change in the code product/reference number of the final substance or any material used in its manufacture.	**Conditions**	**Documents**	**Type of change**
	1	1	Annual notification
Conditions			
1. The change does not regard the quality of the final substance or the concerned material.			
Documents			
1. Approved and proposed code product / reference number.			

2 – Quality Changes

2.1 Change in the manufacturer of a starting material used in the manufacturing process of the API.	**Conditions**	**Documents**	**Type of change**
1. The proposed manufacturer of the starting material is part of the same group as the currently approved manufacturer.	1, 2	1, 2, 3, 4	Immediate notification
2. The proposed manufacturer of the starting material is not part of the same group as the currently approved manufacturer.	1, 2	1, 2, 3, 4	Minor
3. The proposed manufacturer of the starting material uses a different route of synthesis or manufacturing conditions which impact the specifications of the starting material.		1, 3, 4	Minor
4. The proposed manufacturer of the starting material uses a different route of synthesis or manufacturing conditions which impact the specifications of the final substance.		Art. 57, §3º	Major*
Conditions			
1. The specifications of the starting material are identical to those already approved.			
2. The API is not a sterile substance.			
Documents			
1. A declaration from the DIFA holder that the specifications of the API are the same as those already approved.			

2. A declaration from the DIFA holder that the specifications and the quality control procedures of the starting material are the same as those already approved. If a different route of synthesis is retained for the new supplier, the synthetic flowchart of how the starting material is obtained should be provided.
3. A list (with name and complete address) of all current approved manufacturers/sites versus all proposed manufacturers sites in the current submission.
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed manufacturers/sites.
* If the quality characteristics (eg. physical characteristics, impurity profile) of the API are changed in a way that stability may be compromised, comparative stability data are required, on the API before and after the change.

2.2 Change in the manufacturer of an intermediate	**Conditions**	**Documents**	**Type of change**
1. The proposed manufacturer of the intermediate is part of the same group as the currently approved manufacturer.	1,2	1, 2, 3, 4, 5	Immediate notification
2. The proposed manufacturer of the intermediate is not part of the same group as the currently approved manufacturer.	1, 2	1, 2, 3, 4, 5	Minor
3. The proposed manufacturer of the intermediate uses a substantially different route of synthesis or manufacturing conditions which are likely to change the specifications (qualitative and/or quantitative impurity profile) of the API (e.g. change in synthetic strategy, new reagents, solvents, materials are introduced into the synthesis)	3	Art. 57, §3º	Major*
Conditions			
1. The specifications and the route of synthesis (including in-process controls, methods of analysis of all materials used) of the intermediate are identical to those already approved.			
2. The API is not a sterile substance.			
3. When a substantially different route of synthesis or manufacturing conditions is used the new manufacturer will replace the current manufacturer. The addition of an alternative process into a file where the synthetic route is different i.e. different synthetic intermediates, and even when the impurity profile of the final substance is equivalent, is not acceptable and a separate DIFA is needed.			
Documents			
1. A declaration from the DIFA holder that the specifications of the API are the same as those already approved.			
2. A declaration from the DIFA holder that the synthetic route/manufacturing process (or in case of herbal material, where appropriate, the method of preparation, geographical source and production), the specifications and the quality control procedures of the intermediate are the same as those already approved.			
3. A list (with name and complete address) of all current approved manufacturers/sites versus all proposed manufacturers/manufacturing sites in the current submission.			
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed manufacturers/sites.			
5. Declarations that the manufacture of the intermediate is conducted according to the DIFA and GMP and that the manufacturer is willing to be inspected (art. 9, item I). Information on sources and specification of starting materials used by the new intermediate manufacturer.			
*If the quality characteristics (eg. physical characteristics, impurity profile) of the API are changed in a way that stability may be compromised, comparative stability data are required, on the API before and after the change.			

2.3 Change in the manufacturer of the final substance (including where relevant quality control testing sites)	**Conditions**	**Documents**	**Type of change**
1. The proposed manufacturer (manufacturing site/workshop) of the API is part of the same group as the currently approved manufacturer.	1, 2	1, 2, 3, 4	Immediate notification

2. The proposed manufacturer (manufacturing site/workshop) of the API is not part of the same group as the currently approved manufacturer.	1, 2	1, 2, 3, 4	Minor
3. Addition or replacement of a quality control testing site for the API.	2, 3	1	Immediate notification
4. Addition or replacement of an alternative sterilisation site for the final substance using a standard method of sterilisation (listed in pharmacopoeias recognized by ANVISA).	1	1, 2, 5	Minor
5. Introduction of a new (additional) site of micronization.	1, 2, 4, 5	1, 2, 3, 4	Immediate notification
Conditions			
1. The specifications (including in-process controls, methods of analysis of all materials used), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.			
2. The API is not a sterile substance.			
3. Method transfer from the current to the new site has been successfully completed.			
4. The particle size specification of the final substance and the corresponding analytical method remain the same and are already included on the CADIFA.			
5. A micronization site is already approved (included on the CADIFA).			
Documents			
1. A list (with name and complete address) of all current approved sites versus all proposed manufacturers/manufacturing sites in the current submission.			
2. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the API from the approved and proposed manufacturers/sites.			
3. Declarations that the manufacture of the API is conducted according to the DIFA and GMP and that the manufacturer is willing to be inspected (art. 9, item I). Information on sources and specification of starting materials used by the new intermediate manufacturer.			
4. A declaration from the DIFA holder that the synthetic route/manufacturing process (or in case of herbal material, where appropriate the method of preparation, geographical source and production), quality control procedures and specifications of the API are the same as those already approved.			
5. Declaration that the sterilization is conducted according to the DIFA and GMP and that the sterilization site is willing to be inspected (art. 9, inciso I).			

2.4 Changes in the manufacturing process of an intermediate or the API	**Conditions**	**Documents**	**Type of change**
1. Minor change in the manufacturing process of an intermediate or the API that is not expected to impact the quality, safety or control strategy of the API	1, 2	1, 2, 3	Annual notification
2. Any other minor changes in the manufacturing process of an intermediate or the API e.g. introduction of recovery procedures, addition of a solvent in a synthesis step excluding final purification and when this solvent is already used elsewhere in the approved process, changes to the process resulting in a new grade of the substance including micronisation, change in source of a material used in the preparation of the final substance from a TSE risk material to a vegetable, synthetic, or non-TSE risk material.		1, 2, 4, 5, 6	Minor

3. Replacement of the manufacturing process with substantial changes likely to change the qualitative and/or quantitative impurity profile of the API also including the introduction of a 'telescoped process' (where multiple chemical transformations are run without isolation of intermediates) or the introduction of new technology (e.g. 'flow chemistry' or 'continuous manufacturing process technology).	3	Art. 57, §3º	Major*
4. Change in the manufacturing process of an intermediate or the API concerning the sterilisation step(s), including changes in batch size of a sterile substance.		Art. 57, §3º	Major*
5. Changes in the manufacturing process of a herbal substance related to geographical source or production.		Art. 57, §3º	Major*
Conditions			
1. The specifications of the API or intermediates are unchanged and there is no adverse change in qualitative and quantitative impurity profile of the API.			
2. The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process (eg, non-significant adjustments to operating conditions, non-significant changes in equipment, addition of a reprocessing step, i.e. the direct repetition of an approved step, repetition of washing/purification operations within the same step, changes/upgrades in equipment except for sterile grade material). In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.			
3. When a substantially different route of synthesis or manufacturing conditions is proposed the new route of synthesis will replace the current route. The addition of an alternative process into a file where the synthetic route is substantially different, and even when the impurity profile of the final substance is equivalent, is not acceptable and a separate application is needed.			
Documents			
1. Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) of the API manufactured according to the approved and proposed process.			
2. A direct comparison of the approved and the proposed processes.			
3. A declaration from the DIFA holder that the specifications of the API the same as those already approved.			
4. Specifications from the DIFA holder for the proposed source of the material.			
5. If relevant, a declaration from the manufacturer of the material that it is purely of vegetable, synthetic or non-TSE risk origin (specifying the origin).			
6. If relevant, a declaration from the DIFA holder that there is no change in the manufacturing process of the API and that the specifications of the API remain the same.			
* If the quality characteristics (eg. physical characteristics, impurity profile) of the API are changed in a way that stability may be compromised, comparative stability data are required, on the API before and after the change.			

2.5 Change in batch size of API or intermediate	**Conditions**	**Documents**	**Type of change**
1. Up to 10-fold increase compared to the original approved batch size.	1, 2, 3, 4, 6, 7	1, 2, 3, 4	Annual notification
2. Downscaling down to 10-fold.	1, 2, 3, 4, 5, 6	1, 2, 3, 4	Annual notification
3. More than 10-fold increase compared to the originally approved batch size		2, 3, 5	Minor
Conditions			
1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			
2. Test results of at least two batches of the API complying with the approved specifications should be available for the proposed batch size.			
3. The API is not a sterile substance.			
4. The change does not affect the reproducibility of the manufacturing process.			

5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6. The specifications of the API/intermediates remain the same.
7. The currently approved batch size was not approved via a notification.
Documents
1. The batch numbers of the tested batches having the proposed batch size.
2. Approved and proposed batch size.
3. Updated description of the full process specifying the proposed batch size.
4. A declaration from the DIFA holder that the changes to the manufacturing methods are only those necessitated by scale up / downscaling, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the API/intermediates remain the same.
5. Batch analysis data (in comparative tabular format) on a minimum of one production batch of the final substance manufactured according to both the approved and the proposed sizes.

2.6 Change in test procedure for in-process tests or acceptance criteria applied during the manufacture of API or acceptance criteria for a starting material /reagent/intermediate	**Conditions**	**Documents**	**Type of change**
1. Tightening of the acceptance criteria of in-process tests applied during the manufacture of the API or acceptance criteria for a starting material /intermediate / reagent used in manufacture.	1, 2, 3	1	Annual notification
2. Addition of a new in-process test applied during the manufacture of the API and limit or test for a starting material / intermediate / reagent.	1, 4, 5, 6	1, 2	Annual notification
3. Addition of a new in-process test and limit regarding a critical parameter.		1, 2	Major
4. Deletion of a non-significant in-process test or test for a starting material/intermediate/reagent.	1, 6	1, 3	Annual notification
5. Widening of in-process test acceptance criteria applied during the manufacture of the API or test for a starting material / intermediate / reagent which may have a significant effect on the overall quality of the API.		Art. 57, §3º	Major
6. Deletion of in-process test acceptance criteria applied during the manufacture of the API, which may have a significant effect on the overall quality of the API.		Art. 57, §3º	Major
7. Minor changes/updates in a test procedure.	2, 3, 5, 7	1, 2	Annual notification
8. Change of an acceptance criterion for a mutagenic impurity in a starting material/intermediate/reagent according to the principles and limits of the ICH M7 guideline.		1, 2, 4, 5	Minor
9. Changes to a biological method (including replacement or addition).		1, 2	Minor
Conditions			
1. The change does not result from unexpected events arising during manufacture.			
2. Any change should be within the range of currently approved acceptance criteria.			
3. The test procedure remains the same (e.g. a change in column length or temperature, but not a different type of column or method), or changes in the test procedure are minor.			
4. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
5. The new analytical procedure is not a biological method (does not apply for standard pharmacopoeial microbiological methods).			
6. The test does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the API) or controls for mutagenic impurities, controls for elemental impurities, impurities which are not controlled elsewhere in the process, any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water.			

7. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
Documents
1. Comparative table of approved and proposed in-process tests or limit in starting material/intermediate/reagent.
2. Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
3. Justification/risk assessment from the DIFA holder that the in-process tests are non-significant.
4. Justification/ risk-assessment from the DIFA holder as appropriate showing that the parameter can be deleted or widened according to the principles and limits of the ICH M7 guideline.
5. Batch analysis data on two production batches of the final substance for all tests.

2.7 Change in the tests and/or acceptance criteria of the API	**Conditions**	**Documents**	**Type of change**
1. Tightening of acceptance criteria for the API.	1, 2, 3	1	Immediate notification
2. Addition of a test for the API.	1, 4, 5, 6, 7	1, 2, 3	Immediate notification
3. Deletion of a non-significant test for the API (e.g. deletion of an obsolete parameter).	1, 7	1, 4	Annual notification
4. Deletion of a test which may have a significant effect on the overall quality of the API.		Art. 57, §3º	Major
5. Widening of the approved acceptance criteria for the API in line with the limits of the already adopted monograph/ICH guidelines.		1, 2, 3	Minor
6. Widening of the approved acceptance criteria for the API.		Art. 57, §3º	Major
7. Change of an acceptance criterion for a mutagenic impurity in the API specification according to the principles and limits of the ICH M7 guideline.		1, 3, 5	Minor
8. Introduction or revision (non-editorial changes) of a RMS (Risk management summary) regarding elemental impurities.	8	6	Minor
9. Addition of a test regarding a new grade to be included on the CADIFA (e.g. a micronized material)		1, 2, 3, 7, 8	Minor
Conditions			
1. The change does not result from unexpected events arising during manufacture.			
2. Any change should be within the range of currently approved limits.			
3. The test procedure remains the same, or changes in the test procedure are minor.			
4. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
5. The analytical procedure is not a biological method (does not apply for standard pharmacopoeial microbiological methods).			
6. The change does not concern a mutagenic or an elemental impurity. Any new impurity should be controlled with an appropriate acceptance criterion.			
7. The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the API), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water.			
8. The route of synthesis of the final substance remains unchanged.			
Documents			
1. Comparative table of approved and proposed specifications.			
2. Details of any new analytical method and validation data, where relevant.			
3. Batch analysis data on two production batches of the API for all specification parameters.			

4. Justification/risk-assessment from the DIFA holder as appropriate showing that the parameter is non-significant.
5. Justification/risk-assessment from the DIFA holder as appropriate showing that the parameter can be deleted or widened according to the principles and limits of the ICH M7 guideline.
6. Risk management discussion and summary for elemental impurities.
7. If new sites are involved, a list (with name and complete address) of all current approved sites versus all proposed manufacturers/manufacturing sites in the current submission. Declarations that the manufacture of the API is conducted according to the DIFA and GMP and that the manufacturer is willing to be inspected (art. 9, item I).
8. A declaration from the DIFA holder that the synthetic route/manufacturing process (or in case of herbal material, where appropriate the method of preparation, geographical source and production), quality control procedures and specifications of the API (with the exception for particle size) are the same as those already approved.

2.8 Change in analytical procedure for the API	**Conditions**	**Documents**	**Type of change**
1. Minor changes to an analytical procedure for the API.	1, 2, 3, 4	1, 2	Immediate notification
2. Changes to an analytical procedure (including replacement or addition) for a biological API or changes to a biological method).		1, 2	Minor
3. Changes to an analytical procedure due to a compendial update.	5	3	Annual notification
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. There have been no changes of the total impurities accptance criterion; no new unqualified impurities are detected.			
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
4. The analytical procedure is not a biological method (does not include standard pharmacopoeial microbiological methods).			
5. The change is due to a compendial update.			
Documents			
1. Description of the analytical method and revised specifications.			
2. Comparative validation results, or if justified comparative analysis results showing that the approved test and the proposed one are equivalent.			
3. Additional studies, if applicable.			

2.9 Change in the immediate packaging of the final substance	**Conditions**	**Documents**	**Type of change**
1. Composition.	1, 2, 3	1, 2, 3	Immediate notification
2. Composition for sterile APIs.		Art. 57, §3º	Major*
3. Composition for liquid APIs (non-sterile).		1, 2, 4, 5	Minor
Conditions			
1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
2. Relevant stability studies have been started and relevant stability parameters have been assessed in at least two pilot-scale of industrial scale batches.			
3. The API is not a sterile or liquid.			
Documents			
1. Comparison of the approved and proposed immediate packaging specifications, if applicable.			

2. Appropriate data on the new packaging including a confirmation that the material complies with relevant pharmacopoeial requirements and legislation on plastic materials and objects in contact with foodstuffs.
3. A declaration from the DIFA holder that the required stability studies have been started (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that out of specification results will be communicated immediately to ANVISA along with an action plan.
4. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation on plastic material and objects in contact with foodstuffs.
5. Results of stability studies that have been carried out, on the relevant stability parameters, on at least two pilot or industrial scale batches. Assurance should also be given that the studies will be finalized and that out of specification results will be communicated immediately to ANVISA along with an action plan.
*Comparative stability data is required on at least 2 batches of at least pilot scale of the API.

2.10 Change in the specification parameters and/or limits of the immediate packaging of the API	**Conditions**	**Documents**	**Type of change**
	1, 2, 3	1	Annual notification
Conditions			
1. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the API.			
2. The test procedure remains the same, or changes in the test procedure are minor.			
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documents			
1. Comparative table of current and proposed specifications.			

2.11 Change in the composition / specification of the secondary packaging of the API	**Conditions**	**Documents**	**Type of change**
1. Composition.		1	Immediate notification
2. Specification.	1	1	Annual notification
Conditions			
1. The composition of the secondary packaging of the final substance remains the same.			
Documents			
1. Comparison of the approved and proposed secondary packaging specification/or composition.			

2.12 Change in the re-test period or storage conditions of the API	**Conditions**	**Documents**	**Type of change**
1. Reduction of an approved re-test period.	1	1	Immediate notification
2. Extension of the re-test period of the API and/or change in the storage conditions for the API.		2	Minor
3. Change to more restrictive storage conditions.	1	1	Immediate notification
4. Change to an approved stability protocol.	1, 2	3	Immediate notification
Conditions			

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.
Documents
1. Justification of the reduction of the re-test period or of more restrictive storage conditions.
2. Updated results of stability studies for at least two pilot or production scale batches.
3. Justification for the proposed changes.

2.13 Introduction of a new design space or extension of an approved design space for the final substance, concerning:	**Conditions**	**Documents**	**Type of change**
1. One unit operation in the manufacturing process of the API including the resulting inprocess controls and/or test procedures.		1, 2, 3	Major
2. Tests or analytical procedures for starting materials / reagents / intermediates and/or the API.		1, 2, 3	Major
Documents			
1. The design space has been developed in accordance with the ICH and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the API has been achieved.			
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3. Amendment of the relevant section(s) of the dossier in CTD format.			

2.14 Introduction of a post approval change management protocol related to the API	**Conditions**	**Documents**	**Type of change**
		1, 2, 3	Major
Documents			
1. Detailed description for the proposed change.			
2. Change management protocol related to the API.			
a3. Amendment of the relevant section(s) of the dossier in CTD format.			

2.15 Deletion of an approved change management protocol related to the API	**Conditions**	**Documents**	**Type of change**
	1	1, 2	Immediate notification
Conditions			
1. The deletion of the approved change management protocol related to the API is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol and does not have any effect on the already approved information in the dossier.			
Documents			
1. Justification for the proposed deletion.			
2. Atualização das Seções CTD pertinentes.			

2.16 Changes to an approved change management protocol	**Conditions**	**Documents**	**Type of change**
1. Major changes to an approved change management protocol		Art. 57, §3º	Major

2. Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		1	Minor
Documents			
1. Declaration that any change is within the range of currently approved limits.			

2.17 Implementation of changes foreseen in an approved change management protocol	**Conditions**	**Documents**	**Type of change**
1. The implementation of the change requires no further supportive data	1	1, 2, 3	Immediate notification
2. The implementation of changes requires further supportive data		1 ,2 ,3, 4	Minor
Conditions			
1. The proposed change has been performed fully in line with the approved change management protocol.			
Documents			
1. Reference to the approved change management protocol.			
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol.			
3. Amendment of the relevant section(s) of the dossier in CTD format.			
4. Results of the studies performed in accordance with the approved change management protocol.			

ANNEX III

	Applicant's part	Restricted part	Correspondence with ICH M4Q
Section I - General Information	X		3.2.S.1
Subsection I - Nomenclature	X		3.2.S.1.1
Subsection II - Struture	X		3.2.S.1.2
Subsection III - General Properties	X		3.2.S.1.3
Section II - Manufacture	X	X	3.2.S.2
Subsection I - Manufacturer(s)	X		3.2.S.2.1
Subsection II - Description of Manufacturing Process and Process Controls	(a)	(b)	3.2.S.2.2
Subsection III - Control of Materials		X	3.2.S.2.3
Subsection IV - Controls 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 - Control of Drug Substance	X		3.2.S.4
Subsection I - Specification	X		3.2.S.4.1
Subsection II - Analytical Procedures	X		3.2.S.4.2
Subsection III - Validation of Analytical Procedures	X		3.2.S.4.3
Subsection IV - Batch Analyses	X		3.2.S.4.4
Subsection V - Justification of Specification	X	(g)	3.2.S.4.5
Section V - Reference Standards or Materials	X		3.2.S.5
Section VI - Container Closure System	X		3.2.S.6
Section VII - Stability	X		3.2.S.7
Subsection I - Stability Summary and Conclusions	X		3.2.S.7.1

Subsection II - Post-approval Stability Protocol and Stability Commitment	X		3.2.S.7.2
Subsection III - Stability Data	X		3.2.S.7.3

(a) The applicant's part should contain, at least, the synthetic scheme and simplified description of the manufacturing process, from the introduction of the starting material.

(b) The restricted part should contain all information regarding the manufacturing process.

(c) Information that is also relevant for the marketing authorization holder.

(d) Information that is related to the detailed description of the manufacturing process and that is not relevant for the marketing authorization holder.

(e) For sterile APIs, when there is no subsequent sterilization step in the manufacture of the drug product.

(f) Information about potential impurities that pertain to the sequential procedural narrative can be included in the restricted part, provided that there is unequivocal evidence that the impurity does not need to be controlled in the API.

(g) Information related the the sequential procedural narrative, control of materials and process validation can be included in the restricted part.