Public Consultation no. 1,108 of 18 August 2022

Federal Official Gazette of 24 August 2022

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law no. 9,782 of 26 January 1999, and Article 187, item III, and paragraph 1 of Anvisa Regulation approved pursuant to Collegiate Board Resolution – RDC no. 585 of 10 December 2021, submits to Public Consultation, for comments and suggestions from the general public, a regulation proposal, as decided upon in a meeting held on 17 August 2022, and I, Director-President, determine its publication:

Article 1. The period of 45 (forty-five) days is hereby established for sending comments and suggestions for the proposed text of the Normative Instruction that establishes the modalities and criteria applied for the optimized analysis procedure, which uses the assessments carried out by an Equivalent Foreign Regulatory Authority (EFRA) in the analysis of applications for marketing authorization and post-marketing authorization for medicinal products and biological products, as well as the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA), in Brazilian territory, according to the Annex attached hereto.

Sole paragraph. The period referred to in the caption of this article shall start 7 (seven) days after the date this Public Consultation is published in the Federal Official Gazette.

Article 2. The regulation proposal shall be available in its entirety at Anvisa's website and the suggestions must be sent electronically, by completing the specific electronic form available at: https://pesquisa.anvisa.gov.br/index.php/899929?lang=pt-BR (in Portuguese).

Paragraph 1. Except for the personal data informed by the participants, all contributions received are considered public and of free access by the interested parties, in accordance with the provisions of Law no. 12,527 of 18 November 2011, and shall be available after the public consultation is finished, in its specific page, in the area "*Documentos Relacionados*" ("Related Documents").

Paragraph 2. When completing and sending the electronic form, a participant identification number (ID) shall be made available, which can be used by the user to locate his or her own contribution, and physical documents do not need to be sent by post or delivered in hand to Anvisa.

Paragraph 3. In case the citizen does not have access to computer resources, physical written suggestions may be sent to and received at the following address during the consultation period: Agência Nacional de Vigilância Sanitária/GGMED, SIA trecho 5, Área Especial 57, Brasília-DF, CEP 71.205-050.

Paragraph 4. Exceptionally, international contributions may be sent physically to the following address: Agência Nacional de Vigilância Sanitária/ Assessoria de Assuntos Internacionais – AINTE, SIA trecho 5, Área Especial 57, Brasília-DF, CEP 71.205- 050.

Article 3. When the period established in Article 1 is finished, the Brazilian Health Regulatory Agency shall analyze the contributions and then publish the public consultation result at the Agency's website.

Sole paragraph. As necessary and due to convenience and opportunity reasons, Anvisa may coordinate with organisms and entities involved in the matter, as well as those that have shown interest in the subject, in order to support subsequent technical discussions and the final decision by the Collegiate Board of Directors.

ANTONIO BARRA TORRES

Director-President

ANNEX

PROPOSAL FOR PUBLIC CONSULTATION

Process no.: 25351.900003/2017-42

Subject: Proposal of Normative Instruction that establishes the modalities and criteria applied for the optimized analysis procedure, which uses the assessments carried out by an Equivalent Foreign Regulatory Authority (EFRA) in the analysis of applications for marketing authorization and post-marketing authorization for medicinal products and biological products, as well as the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA), in Brazilian territory.

2021-2023 Regulatory Agenda: Project 1.10

Area responsible for the project: General Office for Medicinal Products – GGMED (initials in Portuguese)

Reporting Director: Antonio Barra Torres

BRAZILIAN HEALTH REGULATORY AGENCY

NORMATIVE INSTRUCTION DRAFT

NORMATIVE INSTRUCTION – IN No. [No.] OF [DAY] [MONTH IN WRITTEN] [YEAR]

Establishes the modalities and criteria applied for the optimized analysis procedure, which uses the assessments carried out by an Equivalent Foreign Regulatory Authority (EFRA) in the analysis of applications for marketing authorization and post-marketing authorization for medicinal products and biological products, as well as the Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA), in Brazilian territory.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, items III and IV of Law

no. 9,782 of 26 January 1999, and Article 187, item VI, and paragraph 1 of Anvisa Regulation approved pursuant to Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Normative Instruction, as decided upon in a meeting held on [date], and I, Director-President, determine its publication:

CHAPTER I

INITIAL PROVISIONS

Section I

Objectives

Article 1. This Normative Instruction establishes the modalities, criteria, and procedures for the marketing authorization and post-marketing authorization for medicinal products and biological products and their active substances, as well as for the issuance of an Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA), by using the analyses carried out by an Equivalent Foreign Regulatory Authority (EFRA).

Section II

Scope

Article 2. The optimized analysis procedure is applicable to medicinal products, active pharmaceutical ingredients (APIs), and biological products and their active substances, having been approved by at least one EFRA.

Sole paragraph. Only the API object of Associated CADIFA petition to Anvisa is eligible for the optimized analysis procedure.

Section III

Definitions

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

I – abbreviated analysis: assessment of a regularization petition based on analyzing the applicability of unedited assessment reports from an EFRA for regulatory decision making in the Brazilian context. Such assessment may partially or totally substitute the need to analyze documents and studies submitted to Anvisa. The documents and studies developed to comply with specific Brazilian context requirements are submitted to ordinary analysis;

II – verified analysis: assessment of a regularization petition based on observing the applicability of results from an EFRA's assessment, which are described in its regulatory documentation, for regulatory decision making in the Brazilian context, including analyses related to legal and regulatory matters, risk-benefit assessment, comorbidities, unmet medical needs, risk management plans, and any quality specificities. The documents and studies that are specific for the Brazilian context, including evidences related to differences in the target population, epidemiology, and other characteristics of the disease, medicinal products used concomitantly,

and other factors that may significantly affect the risk-benefit profile of a product, as well as specific quality parameters, are submitted to ordinary analysis;

III – Equivalent Foreign Regulatory Authority (EFRA): foreign regulatory authority or international organization with regulatory practices aligned with Anvisa's, which is responsible for ensuring that the products authorized for distribution were appropriately assessed and meet recognized standards of quality, safety, and efficacy, and which shall be considered by Anvisa in a practice of regulatory reliance;

IV – Active Pharmaceutical Ingredient Dossier Adequacy Letter (CADIFA, in Portuguese): administrative instrument issued by Anvisa that attests the adequacy of the Drug Master File (DIFA, in Portuguese) to the requirements provided for in Collegiate Board Resolution – RDC no. 359 of 27 March 2020;

V – essential characteristics: attributes of the medicinal product and of the biological product that include their manufacturers, qualitative and quantitative composition, concentration, pharmaceutical form, therapeutic indications, contraindications, posology, target population, administration route, usage, specifications, manufacturing process and the respective production plants involved, API manufacturers, and API and excipient quality levels;

VI – regulatory documentation: reports, opinions, or technical/ legal documents of decision-making, auxiliary, or opinionative nature provided for in the Equivalent Foreign Regulatory Authority's own regulatory instrument, which can be used by Anvisa in the optimized analysis procedure;

VII – 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;

VIII – optimized analysis procedure: technical assessment mechanism facilitated by regulatory reliance practices, which uses the regulatory documentation issued by an Equivalent Foreign Regulatory Authority;

IX – regulatory process: activities, acts, or practices of definitive nature for the regularization of medicinal products, APIs, or biological products and their active substances;

X – regularization: authorization for an API, medicinal product, or biological product to be manufactured, distributed, commercialized, dispensed, and consumed. Health regularization occurs through health marketing authorization or issuance of CADIFA, and includes the alterations made after the initial approval;

XI – active substance: biological active pharmaceutical ingredient that can be subsequently formulated for the manufacture of a particular biological product;

XII – ordinary analysis: assessment of a regularization petition based on the requirements provided for in the applicable Collegiate Board Resolutions – RDCs, without the systematized use of regulatory documentation issued by an EFRA.

CHAPTER II

PROCEDURES FOR THE DESIGNATION OF AN EFRA AND ITS RESPECTIVE REGULATORY DOCUMENTATION

Section I

EFRA designation by Anvisa

Article 4. The institution with similar measures and controls related to the regulatory process adopted by Anvisa is designated as an EFRA, and it must comply with the following requirements:

I – carry out pre- and post-marketing regulatory activities in a manner that is consistent with the ones adopted by Anvisa;

II – have a transparent regulatory system guided by the good regulatory practices, with measures that prevent conflicts of interest;

III – adopt international standards and regulations equivalent to the ones currently adopted by Anvisa applicable to APIs, medicinal products, and biological products and their active substances, particularly the ones established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the World Health Organization (WHO);

IV – have established a formal and practical technical cooperation framework with Anvisa, supported by a Memorandum of Understanding, or equivalent document, that allows the exchange of confidential information;

V – be able to interact with other parties in English, Spanish, or Portuguese; and

VI – be able to submit, or allow the submission of, the required documents and reports provided for in this Normative Instruction for modalities A, B, and C of the optimized analysis process.

Article 5. The EFRA designation shall be ultimately decided upon by Anvisa Collegiate Board of Directors, which shall consider the reports from the technical offices legally responsible for the regularization of medicinal products, APIs, or biological products and their active substances that are object of the matter.

Paragraph 1. The decision referred to in the caption of this article shall be supported by Anvisa's International Affairs Office.

Paragraph 2. Any requirement difference adopted by the EFRA candidate with regards to international standards and regulations must be understood, documented, and approved by Anvisa.

Paragraph 3. The EFRAs approved by Anvisa Collegiate Board are listed in Annex I of this Normative Instruction.

Section II

Admissibility of regulatory documentation issued by the EFRA

Article 6. The EFRA regulatory documentation submitted to support the application for regularization by Anvisa of a medicinal product, API, or biological product and active substances through the optimized analysis procedure must:

I – contain updated data and information that ensure the medicinal product or biological product has essential characteristics identical to the ones approved by the EFRA, also related to quality aspects;

II – have been developed in accordance with standards consistent with the ones used by Anvisa, so as to ensure it has the same scope;

III – be enough to identify the quality level of the medicinal product, API, or biological product and active substances;

IV – be submitted in its entirety, and relevant information for Anvisa's assessment must not be crossed out or omitted;

V – not be subject to any restriction of use by Anvisa;

VI – allow to conclude that the manufacturing process assessed by the EFRA is equivalent to the one being submitted to Anvisa.

Paragraph 1. The impact of potential differences between the medicinal product, the API, or the biological product and its active substances, object of the regularization petition submitted to Anvisa, and the one approved by the EFRA must be justified by the manufacturer or the petitioning company.

Paragraph 2. The justification referred to in Paragraph 1 of this article shall be assessed by Anvisa, and the agency shall decide whether the optimized analysis procedure is applicable to the petition.

Article 7. The applicant may choose the EFRA used as reference for the optimized analysis procedure.

Paragraph 1. The documentation submitted to Anvisa for the purposes of regularization of a medicinal product, API, or biological product and its active substances must include at least the whole updated regulatory documentation of the EFRA used as reference.

Paragraph 2. The regulatory documentation issued by another EFRA may be submitted totally or in part to Anvisa for the purpose of complementing the information from the EFRA used as reference.

CHAPTER III

MODALITIES AND APPLICABILITY OF THE OPTIMIZED ANALYSIS PROCEDURE

Article 8. The modalities of the optimized analysis procedure for the purposes of regularization of medicinal products, APIs, and biological products and their active substances are:

I – Modality A: applicable to the petition for regularization of a medicinal product, API, or biological product submitted to assessment by Anvisa, which has been previously approved by an EFRA for a maximum of 1 (one) year.

II – Modality B: applicable to the petition for regularization of a medicinal product, API, or biological product submitted to Anvisa, which has been previously approved by an EFRA for over 1 (one) year, or that has been qualified for analysis in modality B in Annex II or III of this Normative Instruction.

III – Modality C: applicable to a medicinal product defined as of lower risk, in accordance with the guidelines provided for in a specific guide published by Anvisa.

Sole paragraph. The specific additional requirements related to the possibility of assessment of the regularization petition through modalities A, B, and C are provided for in Annexes II and III of this Normative Instruction.

Article 9. Anvisa may apply the optimized analysis procedure for full or partial assessment of the regularization petition for a medicinal product, API, or biological product.

Paragraph 1. The full assessment referred to in the caption of this article shall occur when the regulatory documentation submitted is enough for the assessment of quality, safety, and efficacy requirements applicable to the medicinal product, API, or biological product.

Paragraph 2. The partial assessment referred to in the caption of this article shall occur when the regulatory documentation submitted is enough for the assessment of one or more complete sessions of the regularization dossier, but not enough for the full analysis of the regularization application.

Article 10. The medicinal product, API, or biological product object of the regularization application for the optimized analysis procedure must be regularized by the EFRA chosen as reference for the application submission to Anvisa.

Paragraph 1. The applicant is responsible for informing Anvisa immediately about all the restrictive regulatory decisions adopted by the EFRA, including, but not limited to:

I – incompliance with the GMP by the productive plants involved in the manufacture of the medicinal product, API, or biological product and its active substances;

II – recall;

III – regularization cancellation;

IV – manufacture discontinuation; or

V – commercialization discontinuation.

CHAPTER IV

PROCEDURES FOR THE SUBMISSION OF APPLICATIONS FOR REGULARIZATION AND POST-REGULARIZATION THROUGH THE OPTIMIZED ANALYSIS PROCEDURE

Section I

Submission of applications for regularization through the optimized analysis procedure

Article 11. The application for regularization of a medicinal product, API, and biological product through the optimized analysis procedure must be submitted with all documents and information established in the specific regulation in force for its respective regulatory category.

Article 12. The application submitted to Anvisa for regularization through the optimized analysis procedure in modalities A and B must be presented, complementarily to the provisions in Article 11, with the following:

I – checklist completed, available in Annex II of this Normative Instruction, when related to medicinal products or biological products;

II – checklist completed, available in Annex III of this Normative Instruction, when related to API;

III – full regulatory documentation issued by the EFRA which the regularization application was submitted to and approved by, and there must be no crossed-out information that may jeopardize Anvisa's assessment;

IV – proof of regularization granted by the EFRA, in force at the moment of application; and

V – list containing the identification of all documents submitted, differentiating the ones previously assessed by the EFRA from those produced for the Brazilian context;

VI – report containing the assessment of the regulatory documentation presented to Anvisa, as well as the confirmation that the medicinal product, API, or biological product and its active substances, object of the regularization application, has essential characteristics identical to the ones approved by the EFRA.

Paragraph 1. The applicant must identify the parts of the report referred to in item VI of this article that contain restricted information provided for in Law no. 12,527 of 18 November 2011.

Paragraph 2. The regularization application qualified for modality A or B shall be submitted to abbreviated analysis.

Article 13. The application submitted to Anvisa for regularization through the optimized analysis procedure in modality C must be presented, complementarily to the provisions in Article 11, with the following:

I – form completed, available in Annex II of this Normative Instruction, when related to medicinal products;

II – copy of the checklist completed, available in Annex III of this Normative Instruction, when related to API;

III – proof of regularization granted by the EFRA, in force at the moment of application; and

IV – list containing the title of all documents submitted, differentiating the ones previously assessed by the EFRA from those produced for the Brazilian context.

Sole paragraph. The regularization application qualified for modality C shall be submitted to verified analysis.

Article 14. The applicant must make a formal request to the pertinent EFRA to authorize the submission of the regulatory documentation in its possession to Anvisa.

Paragraph 1. The regulatory documentation required in this Normative Instruction may be sent to Anvisa, in its entirety or partially, directly by the EFRA when the access to it is not permitted for companies.

Paragraph 2. The applicant is exclusively responsible for the actions provided for in the caption of this article and in Paragraph 1.

Paragraph 3. If the regulatory documentation referred to in Paragraph 1 of this article is not sent, the regularization application shall be submitted, either partially or in its entirety, for ordinary analysis.

Section II

Submission of applications for post-regularization through the optimized analysis procedure

Article 15. The post-regularization alteration that has been approved by the EFRA used as reference in the initial regularization application must be submitted to assessment by Anvisa through the optimized analysis procedure.

Paragraph 1. The applications that are not related to regularized conditions in Brazil are excluded from the provisions in the caption of this article.

Paragraph 2. The post-regularization alteration that has an impact on studies and information presented in the initial regularization application shall be submitted to ordinary analysis, in order to comply with specific requirements in Brazil.

Article 16. The post-regularization alteration that has not been previously approved by the EFRA used as reference in the initial regularization application shall not be permitted.

Paragraph 1. The alterations recorded in a Product Alteration History (PAH) or of immediate implementation are included in the provisions set forth in the caption of this article.

Paragraph 2. Administrative applications or petitions related to the compliance with specific Brazilian regulations are excluded from the provisions set forth in the caption of this article.

Paragraph 3. Post-regularization alterations rejected by an EFRA must not be submitted to Anvisa.

Article 17. The applications referred to in Article 15 must be submitted with the following documents:

I – confirmation that the alteration requested is the same one that was submitted to and approved by the EFRA;

II – summary of the requirements issued by the EFRA and the respective answers given;

III – commitments that have been made to the EFRA; and

IV – document confirming that the post-regularization alteration has been approved by the EFRA.

Paragraph 1. In addition, the applications referred to in the caption of this article must be submitted with the information and documents required in the ordinary analysis of post-regularization applications.

Paragraph 2. The application presented in accordance with the provisions in the caption of this article shall be submitted to abbreviated analysis.

Paragraph 3. Medicinal product post-registration alterations related to quality, previously regularized through the optimized analysis procedure, shall be considered as of immediate

implementation if they comply with the provisions of this Normative Instruction and do not need a new clinical trial or relative bioavailability study.

Paragraph 4. Post-regularization alterations of biological products previously regularized through an optimized analysis procedure, which are classified as “minor alterations” in the terms of Collegiate Board Resolution – RDC no. 413 of 20 August 2020 and Normative Instruction – IN no. 65 of 20 August 2020, shall maintain their immediate implementation status, as long as they are not associated to other post-regularization alterations that require previous approval by Anvisa. In this case, minor alterations may be implemented only after approval through the optimized analysis procedure.

Paragraph 5. CADIFA alteration previously regularized through an optimized analysis procedure, classified as “minor alteration” in the terms of Collegiate Board Resolution – RDC no. 359 of 1 April 2020, shall be of immediate implementation, as long as it is not associated to or resulting from another alteration classified as “major alteration”. In this case, it shall wait for Anvisa’s decision on the optimized analysis procedure for implementation.

Paragraph 6. The alterations referred to in paragraphs 3, 4, and 5 must be recorded in the Product Alteration History (PAH) or submitted individually, in accordance with the provisions in the specific health regulations in force.

Article 18. Post-regularization alteration petitions must be submitted to Anvisa in up to 6 (six) months after approval by the EFRA.

Sole paragraph. In case the individual post-regularization petition is submitted after the period referred to in the caption of this article, the possibility of immediate implementation provided for in paragraphs 3, 4, and 5 of Article 17 is suspended, as well as the analysis periods through the optimized analysis procedure provided for in Article 20.

Section III

Analysis periods

Article 19. The information provided for in the checklist available in Annex II or III of this Normative Instruction shall be assessed for eligibility of the regularization application for the optimized analysis procedure.

Sole paragraph. Once it is considered eligible, the analysis of the application for regularization of medicinal products and biological products shall be completed in up to 150 calendar days from the date the regularization application was submitted.

Article 20. The analysis of post-regularization applications, regardless of the modality applied for the marketing authorization, shall be completed in up to 90 days.

Sole paragraph. The provisions in the caption of this article do not apply to post-regularization alterations of immediate implementation.

Article 21. When the periods provided for in articles 19 and 20 are finished, without an initial manifestation from Anvisa, the regulatory documentation and the other documents submitted in the regularization application shall be submitted to verified analysis.

Sole paragraph. The Agency's manifestation regarding the verified analysis provided for in the caption of this article shall occur in up to 60 days.

Article 22. Anvisa may issue a technical requirement containing requests for clarification about documents and information provided by the applicant.

CHAPTER V

FINAL PROVISIONS

Article 23. The regularization application submitted to Anvisa through ordinary analysis may be re-qualified for the optimized analysis procedure, as long as it is eligible for it in the terms of this Normative Instruction.

Paragraph 1. The alteration in the analysis procedure application referred to in the caption of this article may be submitted by the applicant as a specific addition to the process, as long as this submission is done before the petition analysis starts.

Paragraph 2. Anvisa technical units responsible for the analysis, through the access to documents and reports issued by the EFRA, may choose to apply the optimized analysis procedure, and they must record the adoption of such procedure in the respective process.

Paragraph 3. Article 15 is not applicable to applications or processes analyzed in the terms of Paragraph 2 of this article.

Article 24. The use of the optimized analysis procedure established in this Normative Instruction does not prevent Anvisa from reassessing applications through the ordinary analysis, at any time.

Article 25. The decision on regularization applications submitted through the optimized analysis procedure is an exclusive competence of Anvisa, and it is not bound to decisions and conditions approved by the EFRA.

Article 26. Failure to comply with the provisions contained in this Normative Instruction 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 27. This Normative Instruction enters into force 30 (thirty) days from the date it is published.

ANTONIO BARRA TORRES

Director-President

ANNEXES

ANNEX I – Equivalent Foreign Regulatory Authorities (EFRA) designated by Anvisa.

I – European Medicines Agency – EMA (centralized analyses processes): applicable to medicinal products and biological products;

II – Health Canada: applicable to medicinal products and biological products;

III – World Health Organization – WHO: applicable to APIs and medicinal products;

IV – European Directorate for the Quality of Medicines & HealthCare – EDQM: applicable to APIs;

V – Swiss Agency for Therapeutic Products – Swissmedic: applicable to medicinal products;

VI – Medicines and Healthcare Products Regulatory Agency – MHRA, United Kingdom: applicable to medicinal products and biological products;

VII – US Food and Drug Administration – FDA: applicable to medicinal products and biological products.

ANNEX II – Checklist to assess the eligibility of applications for the marketing authorization for medicinal products and biological products and their active substances through the optimized analysis procedure.

GENERAL INFORMATION	
Marketing authorization process number	
Number(s) of the file(s) the temporary optimized analysis procedure is applied for	
Subject of the application(s)	
Name of the product	
Active pharmaceutical ingredient(s) (API), when it is the case of synthetic or semi-synthetic medicinal products	
Inform the regulatory authority(ies) that approved the regularization application being submitted	

CRITERION	**CHECKLIST**
Administrative information (Applicable to all processes)	
General	
Is the regulatory documentation issued by an equivalent foreign regulatory authority (EFRA) designated by Anvisa?	☐ **Yes.** Inform the name of the EFRA chosen as reference and the date of approval: Name of the EFRA:_____ Date of approval: _____ ☐ **No.** The application is not eligible for the optimized analysis procedure.
	☐ **No.** Informative item.

Is there any complementary information issued by another EFRA, which has been attached to the application?	☐ **Yes.** Inform the name of the EFRA chosen as reference and the date of approval: Name of the EFRA:_____ Date of approval: _____
Does the marketing authorization/ regularization applicant belong to the same corporate group as the holder of the marketing authorization/ regularization approved by the EFRA?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach an authorization letter from the marketing authorization/ regularization holder confirming that the applicant acts in accordance with the rights deriving from the marketing authorization/ regularization holder and the holder agrees the procedure is applied in Brazil.
Does the dossier meet the application criteria listed below? 1 – The regulatory documentation issued by the EFRA refers to an assessment for a definitive approval for the commercialization of the medicinal product or biological product, that is, it was not provisionally or conditionally approved. 2 – The regulatory documentation issued by the EFRA is complete, in Portuguese, English, or Spanish, and it was not edited or crossed out. 3 – Another application for the marketing authorization for the medicinal product or biological product object of this application was not denied, rejected, refused, or withdrawn in any country.	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **It does not meet item 3 only.** Inform the countries and attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. ☐ **It does not meet item 1 or 2.** The application is not eligible for the optimized analysis procedure.
Was another application for the marketing authorization for the medicinal product or biological product object of this application rejected or is it commercialized with a court order in any country?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** Inform the country and attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. Country: _____
International alignment of directives	
Does the regulatory documentation issued by the EFRA refer to or was it elaborated in accordance with the guides published by the ICH or the WHO?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. If eligible, the optimized analysis procedure shall be applied in modality B*.
Does the regulatory documentation issued by the EFRA refer to or was it elaborated in	☐ **Yes.** The application is eligible for the optimized analysis procedure.

accordance with non-clinical directives published by the ICH or the WHO?	☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Does the regulatory documentation issued by the EFRA refer to or was it elaborated in accordance with the safety and efficacy directives published by the ICH or the WHO?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Does the report refer to a specific directive or guide different from ICH or WHO references?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** It is necessary to attach clarifications to identify and justify the divergences between the directives or guides adopted by the EFRA and ICH or WHO directives. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Quality	
Characteristics of the medicinal product or biological product object of the application	
Does the API, medicinal product, or biological product object of the application have essential characteristics identical to the characteristics of the one approved by the EFRA and described in the EFRA regulatory documentation presented, regarding the criteria described below? 1 – Dosage; 2 – Concentration; 3 – Formulation (API or active substance and excipients); 4 – Manufacturers (starting material, intermediates, API or active substance, intermediate product, medicinal product, or biological product); 5 – Manufacturing process (active substance, intermediate product, medicinal product, or biological product); 6 – Cell and viral banks, when applicable; 7 – Molecular characterization, when applicable; 8 – Specifications of release and stability of the biological product and its active substances.	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** The application is not eligible for the optimized analysis procedure.
Was the generic/ similar medicinal product developed based on the reference medicinal product elected by Anvisa?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** The application is eligible for the optimized analysis procedure in modality B*. ☐ **Not applicable.** It is not a generic medicinal product.

Additional manufacturing sites	
Are additional manufacturing sites (that is, not included in the dossier sent to the EFRA) indicated in this submission to Anvisa?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Is the additional site solely for the stages of labeling, secondary packaging, or release of batches for distribution?	☐ **Not applicable.** There are no additional manufacturing sites. ☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** Other stages are carried out at the additional sites. It is necessary to attach clarifications describing the additional stages. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. If eligible, the optimized analysis procedure shall be applied in modality B, but the periods of time provided for in this regulation shall not be applicable.
Have validation data, including batch analyses, been provided for the additional sites?	☐ **Not applicable.** There are no additional manufacturing sites. ☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** The application is not eligible for the optimized analysis procedure. Note: additional assessment may be necessary.
Good Manufacturing Practices (GMP)	
Do all manufacturing sites indicated have a valid Good Manufacturing Practices Certificate (GMPC) issued by Anvisa?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** The application is eligible for the optimized analysis procedure, as long as the inspection(s) has (have) already been scheduled with Anvisa. The applicant must present the scheduling confirmation. ☐ **Not applicable.** The GMPC issued by Anvisa is not required by the legislation in force. It is necessary to attach the documentation issued by the EFRA, confirming the production plant's regular status at the EFRA with regards to the Good Manufacturing Practices.
Stability, shelf life, and packaging	
	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No**, because the medicinal product or biological product object of the application must not be stored in environment temperature (e.g., controlled temperature).

Were the stability studies assessed by the EFRA for granting shelf life conducted according to the climate zone (IVb)?	The application is eligible for the optimized analysis procedure. ☐ **No**, but the applicant is sending zone IVb stability studies. The application is eligible for the optimized analysis procedure. ☐ **No.** The application is not eligible for the optimized analysis procedure.
Are the proposed shelf life, the shelf life in use, and the storage conditions identical to the ones accepted by the EFRA?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications on the specific shelf life proposed. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. If eligible, the optimized analysis procedure shall be applied in modality B*.
Information on the API regularization	☐ **Not applicable (check this option if the product object of analysis does not have a synthetic or semi-synthetic API liable to regularization).**
Will the API regularization be carried out through the optimized analysis procedure?	☐ **Yes.** The DIFA holder must complete Annex III and submit it in the API regularization process. ☐ **No.** Include a copy of CADIFA (or present "CADIFA Process Notification") and the additional information in the medicinal product marketing authorization process.
Safety and efficacy	
Indications and instructions for use	
Are the proposed therapeutic indications equivalent to the ones approved by the EFRA, including posology, target population, route of administration, and conditions of use?	☐ **No.** The application is not eligible for the optimized analysis procedure. ☐ **Yes.** Inform the hyperlink to access the EFRA's approval public report: _____
Are the proposed indications identical to the proposed indications of the reference medicinal product or comparator product in Brazil?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. ☐ **Not applicable.** It is not a generic medicinal product or a biossimilar product.
Package leaflets	
Does the EFRA's regulatory documentation provide the safety and efficacy information required for the elaboration of the Brazilian package leaflet text, considering the requirements in RDC 47/2009?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications.
Clinical studies	☐ **Not applicable (check this option if clinical studies have not been conducted for**

	the product object of analysis (e.g., generic medicinal products)).
Did the medicinal product have a clinical study, or part of it, conducted in Brazil?	☐ **No.** ☐ **Yes.** Inform which study phase was conducted.
Are there minor updates for main studies or support studies available that were not considered in the EFRA's approval and support the proposed indication?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** It is necessary to inform details, such as notes on the proposed package leaflet with references to relevant documentation. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Is there any additional information available relevant to the risk-benefit ratio of the indication approved by the EFRA (for example, additional Periodic Safety Update Report or long-term safety study available since the approval)?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** It is necessary to submit the additional information. The application is eligible for the optimized analysis procedure in modality B* and the periods of time are not applicable. In case of post-marketing authorization, the optimized procedure is not applicable.
Have new clinical studies been conducted or has new clinical evidence been obtained since the medicinal product or biological product was assessed by the EFRA?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** The application is not eligible for the optimized analysis procedure.
Are there bridging studies designed to adjust the medicinal product or biological product to the Brazilian population?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** Only the quality aspects are eligible for the optimized analysis procedure.
Generic Medicinal Products	☐ **Not applicable (check this option if the product object of analysis is not a generic medicinal product).**
Was the reference medicinal product used in the comparability studies presented to the EFRA a medicinal product currently granted marketing authorization in Brazil?	☐ **No.** Informative item. ☐ **Yes.** Inform the marketing authorization number in Brazil. Marketing authorization number: _____
Did the dossier submitted to the EFRA contain bioequivalence and bioavailability (biopharmaceutical) data?	☐ **Yes.** Informative item. ☐ **No.** It is necessary to attach clarifications on the lack of biopharmaceutical data in the dossier submitted to the EFRA.
Is a reference medicinal product granted marketing authorization in Brazil used in bioequivalence and bioavailability (biopharmaceutical) studies?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** The application is not eligible for the optimized analysis procedure. ☐ **Not applicable.** The product is bio-exemptible , in accordance with the Brazilian legislation in force. It is necessary to attach clarifications. Subject to assessment by

	Anvisa of the eligibility for the optimized analysis procedure. ☐ **Not applicable.** The reference medicinal product considered by the EFRA and the reference medicinal product in Brazil are manufactured in a single location for global distribution. It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. If eligible, the optimized analysis procedure shall be applied in modality B*.
Biosimilar medicinal products	☐ **Not applicable (check this option if the product object of analysis is not a biosimilar medicinal product).**
Is the comparator product representative of the Brazilian product?	☐ **Yes.** Inform the marketing authorization number in Brazil. Marketing authorization number: _____ ☐ **No.** The application is not eligible for the optimized analysis procedure.
Risk Management Plan (RMP)	☐ **Not applicable (check this option if the Risk Management Plan (RMP) is not required in accordance with the Brazilian legislation in force).**
Is any of the documents below included in the application submitted: I – RMP approved by the EFRA; II – Global/ General RMP; or	☐ **Yes.** Inform the names of the documents. ☐ **No.** The application is not eligible for the optimized analysis procedure.
Is an RMP specific for Brazil included in the application submitted?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Is a current RMP approved by the EFRA included in the application submitted?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Are there issues related to risk management, specific to the Brazilian scenario, included in the application submitted to Anvisa?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Is the risk management system proposed for Brazil equivalent to the one approved by the EFRA?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the

	eligibility for the optimized analysis procedure.
Does the EFRA's report include an assessment of the RMP presented (either its current or previous version) and comments on the adequacy of the Summary of Safety Concerns?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Does the EFRA's report include an assessment of an RMP, proposing a risk management system equivalent to the one proposed for Brazil (including equivalent pharmacovigilance and risk minimization activities, as well as considerations on the adequacy of an equivalent summary of safety concerns)?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** It is necessary to attach clarifications. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Conclusion	
In any of the questions in this checklist, was an answer checked indicating the application is not eligible for the optimized analysis procedure?	☐ **Yes.** The process is not eligible for the optimized analysis procedure. ☐ **No.** Answer the next questions.
Is the medicinal product or biological product classified as a minor risk product, in accordance with the provisions in Item III of Article 8?	☐ **Yes.** The modality applicable to the petition shall be C. It is not necessary to answer the other questions in this section. ☐ **No.**
Was the medicinal product or biological product approved by the EFRA over 1 year ago?	☐ **Yes.** The modality applicable to the petition shall be B. It is not necessary to answer the other questions in this section. ☐ **No.**
In any of the questions in this checklist, was an answer checked leading the application to the optimized analysis procedure in modality B?	☐ **Yes.** The modality applicable to the petition shall be B. ☐ **No.** The modality applicable to the petition shall be A.

Based on the checklist above, I hereby formalize the submission of the dossier through the optimized analysis procedure in Modality: ( ) A ( ) B ( ) C

I am aware that Anvisa may, in accordance with the technical assessment of the information provided, reclassify the modality of the application, or adopt the ordinary analysis.

I hereby declare that I have authorization from the EFRA(s) to submit to Anvisa all the regulatory documentation comprising this protocol, in accordance with the provisions of Article 14 of this Normative Instruction.

By completing and signing this form, I authorize Anvisa, if necessary, to contact the EFRA and exchange the information relating to my application.

Date: __/__/____

Name: _____

Signature: _____

Annex III – checklist to assess the eligibility of applications for CADIFA through the optimized analysis procedure.

GENERAL INFORMATION	
Application process number:	
Number(s) of the file(s) the temporary optimized analysis procedure is applied for	
Subject(s) of the application(s)	
Name of the API	

CRITERION	**CHECKLIST**
General	
Was the submitted regulatory documentation issued by an equivalent foreign regulatory authority (EFRA) designated by Anvisa?	☐ **No.** The application is not eligible for the optimized analysis procedure. ☐ **Yes.** Inform the name of the EFRA and the date it was approved by Anvisa: Name of the EFRA:_____ Date of approval: _____ If applicable, present a letter authorizing the exchange of regulatory documentation by the EFRA with Anvisa.
Does the EFRA's regulatory information meet the following general application criteria? I – The regulatory documentation refers to an assessment for a definitive regularization of the API (that is, it is not a provisional or conditional approval). II – The regulatory documentation is complete, in Portuguese, English, or Spanish, and it was not edited or crossed out.	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** The application is not eligible for the optimized analysis procedure.
Was the application for regularization of the API object of this petition rejected or is it commercialized with a court order in any country?	☐ **No.** The application is eligible for the optimized analysis procedure. ☐ **Yes.** Inform the country details on the case: _____ Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure.
Drug Master File (DIFA, in Portuguese)	
Is the DIFA approved by an EFRA?	☐ **No.** The application is not eligible for the optimized analysis procedure. ☐ **Yes.** Inform the name of the EFRA and the date the DIFA was approved by the EFRA. In

	addition, inform the Version of the DIFA submitted to the EFRA. Name of the EFRA: _____ Date of approval: _____ Version of the DIFA submitted to the EFRA: _____
Is there a copy attached of: I – the latest approved version of a valid Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP), issued by EDQM, completed by its holder in the name of the medicinal product marketing authorization/ post-marketing authorization applicant; or II – the latest approved version of a valid Confirmation of API prequalification (CPQ), issued by the WHO, completed by its holder in the name of the medicinal product marketing authorization/ post-marketing authorization applicant; or III – equivalent document confirming the approval by an EFRA listed in Annex I of this Normative Instruction.	☐ **Yes.** Inform the document version and its respective issuer. Document version: _____ Issuer: _____ ☐ **No.** The application is not eligible for the optimized analysis procedure. ☐ The API optimized analysis procedure shall not use such documents.
Are the quality information of the DIFA submitted to Anvisa (part 3.2.S) identical to the quality information of the DIFA currently approved by the EFRA?	☐ **Yes.** The application is eligible for the optimized analysis procedure. ☐ **No.** In case this option is checked, indicate on the list below the sections with identical information, if any. Subject to assessment by Anvisa of the eligibility for the optimized analysis procedure. If eligible, the optimized analysis procedure shall be applied in modality B*. General Information (3.2.S.1) ☐ Nomenclature (3.2.S.1.1) ☐ Structure (3.2.S.1.2) ☐ General Properties (3.2.S.1.3) Manufacture (3.2.S.2) ☐ Manufacturer(s) (3.2.S.2.1) ☐ Description of the Manufacturing Process and In-process Controls (3.2.S.2.2) ☐ Control of Raw Materials (3.2.S.2.3) ☐ Control of Critical Stages and Intermediates (3.2.S.2.4) ☐ Process Validation (3.2.S.2.5) ☐ Manufacturing Process Development (3.2.S.2.6)

	Characterization (3.2.S.3) ☐ Structure Elucidation and Other Characteristics (3.2.S.3.1) API Quality Control (3.2.S.4) ☐ Specification (3.2.S.4.1) ☐ Analytical Methods (3.2.S.4.2) ☐ Validation of Analytical Methods (3.2.S.4.3) ☐ Analysis of Batches (3.2.S.4.4) ☐ Justification for Specification (3.2.S.4.5) ☐ Materials and Reference Chemical Substances (3.2.S.5) ☐ Packaging (3.2.S.6) Stability (3.2.S.7) ☐ Stability Summary (3.2.S.7.1) ☐ Protocols and Post-submission Commitments (3.2.S.7.2) ☐ Stability Data and Reports (3.2.S.7.3) For unchecked sections, present Comparative Table (Annex 8 of the Application Form), for assessment of the eligibility for the optimized analysis procedure.
Conclusion	
In any of the questions in this checklist, was an answer checked indicating the application is not eligible for the optimized analysis procedure?	☐ **Yes.** The process is not eligible for the optimized analysis procedure. ☐ **No.** Answer the next questions.
Is the API classified as a minor risk product, in accordance with the provisions in Item III of Article 8, and was (were) the production plant(s) inspected by Anvisa to verify quality aspects?	☐ **Yes.** The modality applicable to the petition shall be C. It is not necessary to answer the other questions in this section. ☐ **No.** Answer the next question.
Was the API approved by the EFRA over 1 year ago?	☐ **Yes.** The modality applicable to the petition shall be B. It is not necessary to answer the other questions in this section. ☐ **No.** Answer the next question.
In any of the questions in this checklist, was an answer checked leading the application to the optimized analysis procedure in modality B?	☐ **Yes.** The modality applicable to the petition shall be B. ☐ **No.** The modality applicable to the petition shall be A.

Based on the checklist above, I hereby formalize the submission of the dossier through the optimized analysis procedure in Modality: ( ) A ( ) B ( ) C

I am aware that Anvisa may, in accordance with the technical assessment of the information provided, reclassify the modality of the application, or adopt the ordinary analysis.

I hereby declare that the API approved by the EFRA has the same quality level as the API in this application, including the following:

1. Manufacturing process (including parameters and in-process controls);

2. Manufacturing sites;

3. Specification of raw materials, including the specification of start materials;

4. Suppliers and route for obtention of start materials;

5. Intermediate specification and analytical methods;

6. API specification and analytical methods;

7. API solid phase properties;

8. Packaging;

9. Stability data;

10. Information level (open part) available to the applicants;

11. Any other parameters that may have a potential impact on the API quality.

I hereby declare that the DIFA meets the international quality guidelines adopted by Anvisa, particularly the following:

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;

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;

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.

I hereby declare that I have authorization from the EFRA(s) to submit to Anvisa all the regulatory documentation comprising this protocol, in accordance with the provisions of Article 14 of this Normative Instruction.

By completing and signing this form, I authorize Anvisa, if necessary, to contact the EFRA and exchange the information relating to my application.

Date: __/__/____

Name: _____

Signature: _____