NORMATIVE INSTRUCTION - IN Nº 289, OF MARCH 20, 2024

Establishes, under the terms of Resolution - RDC nº 741/2022, the criteria applied for the optimized analysis procedure where assessments conducted by Equivalent Foreign Regulatory Authority (AREE) are used for analysis of marketing authorization or post-approval change applications of drug products, biological products, vaccines and the letter of suitability of the active pharmaceutical ingredient (CADIFA) in national territory.

CHAPTER I
PRELIMINARY PROVISIONS

Section I
Objectives

Art. 1º This Normative Instruction establishes, under the terms of Resolution - RDC nº 741/2022, the criteria and procedures for approval of marketing authorization and post-approval change of drug products, vaccines, biological products, and their active substances, and letter of suitability of the active pharmaceutical ingredient (CADIFA), by using analyses carried out by Equivalent Foreign Regulatory Authority (AREE).

Section II
Scope

Art. 2º The optimized analysis procedure is applicable to the drug product, active pharmaceutical ingredient (API), vaccine and biological product, and their active substances approved by at least one AREE.

§1º Only the API in an associated CADIFA application submitted to ANVISA is eligible for the optimized analysis procedure.

§2º The optimized analysis procedure is applicable to studies of therapeutical equivalence approved by an AREE, regardless of certification or qualification of the laboratory or center by ANVISA, as long as the comparative drug product used in the study is accepted by ANVISA under the terms of Resolution - RDC n° 35/2012, or normative instructions that come to replace it.

Section III
Definitions

Art. 3º For the purposes of this Normative Instruction, it is considered:

I - verified analysis: verification of the applicability of results from an AREE's assessment 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.

II - Equivalent Foreign Regulatory Authority (AREE): 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;

III - Letter of Suitability of the Active Pharmaceutical Ingredient (CADIFA): administrative instrument that attests the compliance of the API with the requirements of the Resolution - RDC nº 359/2020, or in normative instruments that come to replace it;

IV - Associated CADIFA: refers to a CADIFA application associated to a marketing authorization or post-approval change application of synthetic or semisynthetic drug products submitted to Anvisa, as part of marketing authorization or post approval change applications;

V - Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP): administrative instrument issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) that certifies that the quality of the API to be used in marketing authorization application is appropriately controlled according to the monographs of the European Pharmacopoeia, with addition of tests if necessary;

VI - Essential characteristics: attributes of the drug product, vaccines and biological product that include their manufacturers, qualitative and quantitative composition, concentration, dosage form, therapeutic indications, contraindications, posology, target population, administration route, usage, specifications, manufacturing process and the respective production plants involved, API manufacturers, and quality grade of API and excipients;

VII - Instructional documentation: reports, briefings, opinions, or technical/legal documents of decision-making, auxiliary, or opinionative nature in a AREE's own regulatory instrument, which can be used by Anvisa in the optimized analysis procedure;

VIII - 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.

IX - Optimized analysis procedure: technical assessment mechanism facilitated by regulatory reliance practices, which uses the instructional documentation issued by an AREE;

X - Regulatory process: activities, acts, or practices of finalistic nature for regularization of drug products, vaccine, API, or biological product and their active substances;

XI - regularization: authorization for an API, drug product, vaccine, or biological product to be manufactured, distributed, commercialized, dispensed and consumed. Health regularization occurs through marketing authorization or issuance of CADIFA, and includes post-regularization changes made after the initial approval.

XII - active substance: biological active pharmaceutical ingredient that can be subsequently formulated for the manufacturing of a particular biological product; and

XIII - ordinary analysis: assessment of a regularization application without the systematized use of instructional documentation issued by an AREE.

CHAPTER II
PROCEDURES FOR DESIGNATION OF AN AREE AND ITS RESPECTIVE INSTRUCTIONAL DOCUMENTATION

Section I
ANVISA designation of the AREE

Art. 4º It is designated as AREE the institution that presents similarity of standards and controls related to the regulatory process adopted by ANVISA and meets all the following requirements:

I - conduct regulatory activities of pre and post marketing surveillance, consistent with those adopted by ANVISA;

II - have a transparent regulatory system guided by good regulatory practices, with measures that prevent conflict of interest;

III - adherence to the same international standards and guidelines currently adopted by ANVISA, applicable to APIs, drugs products, vaccines, and biological products and their active substances, particularly those 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 structure of technical cooperation with ANVISA, sustained by Memorandum of Understanding, or equivalent document, that enables exchange of confidential information;

V - can interact in English, Spanish or Portuguese; and

VI - is not prohibited to submit or allow the submission of the necessary documents and reports requested by this Normative Instruction to apply the optimized analysis process.

Art. 5º The designation of the AREE will be decided, ultimately, by the Board of Directors of ANVISA, which will consider the technical opinions of offices regimentally responsible for the regularization of drug product, API, vaccine or biological product and their active substances included in the decision scope.

§1º The decision referred to in the caption will be subsidized by ANVISA's International Affairs Office.

§2º Any difference in the requirements adopted by the applicant to AREE compared to international standards and guidelines must be well understood, documented, and approved by ANVISA.

§3º The AREEs approved by the Board of Directors of ANVISA are listed in this Normative Instruction's annex I.

§4º The Annex I will be updated according to the regulatory flow and periodical updates.

Section II
Admissibility of the AREE instructional documentation

Art. 6º The AREE instructional documentation submitted to support the regularization application of a drug product, API, vaccine or biological product and their active substances at ANVISA through the optimized analysis procedure must:

I - include updated data and information that ensure the drug product, vaccine, or biological product have essential characteristics identical to the ones approved by the AREE, also regarding to their quality aspects;

II - be able to identify the quality grade of the API, in case of CADIFA; and

III - be submitted in its completeness, without any relevant information for Anvisa's assessment being censored or omitted.

§1º The impact of eventual differences between the drug product, API, vaccine or biological product and their active substances submitted to ANVISA and the one approved by the AREE must be justified by the manufacturer or applicant.

§2º The justification referred to in Paragraph 1º will be assessed by ANVISA, which shall decide if the optimized analysis procedure may be applied to the application.

§3º When relevant information provided in item III are censored or omitted in the AREE documentation, a declaration can be provided, signed by the holder of the regularization product in the AREE and by the legal representative of the company that is submitting the application to ANVISA, containing the missing information completely and accurately.

Art. 7º The applicant may designate the AREE to be used as reference for the optimized analysis procedure.

Art. 8º The documentation submitted for the purpose of regularization of drug product, API, vaccine or biological product and their active substances, must contain, at least, all instructional documentation updated of the AREE used as reference, including documentations of post-regularization change application that may have occurred before submission to ANVISA, when applicable.

Single paragraph. Part or all the instructional documentation issued by a second AREE can be submitted to ANVISA for the purposes of complementing the information of the AREE used as reference.

CHAPTER III
APPLICABILITY OF THE OPTIMIZED ANALYSIS PROCEDURE

Art. 9º The requirements for eligibility of regularization applications, to be submitted to analysis through optimized procedure are described in detail in Annexes II and III of this Normative Instruction.

Art. 10. Regularization applications of drugs products, API, vaccines or biological products will be subjected to verified analysis, if they meet the eligibility criteria for the optimized procedure.

Single paragraph. 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, drug products concomitantly used, and other factors that may significantly affect the benefit-risk profile of a product, as well as specific quality parameters must be submitted to the ordinary analysis.

Art. 11. The optimized procedure can be completely or partially applied.

§1º The optimized procedure will be applied completely when the instructional documentation submitted is sufficient for the assessment of quality, safety, and efficacy requirements applicable to the drug product, API, vaccine or biological product.

§2º The optimized procedure will be applied partially when the instructional documentation submitted is sufficient for the assessment of one or more parts of the dossier but is not sufficient for a complete analysis of the regularization application.

Art. 12. The drug product, API, vaccine or biological product, object of the regularization application through optimized analysis procedure, must be regularized by the AREE chosen as reference for submission of the request to ANVISA.

Single paragraph. The applicant is responsible for immediately notifying ANVISA regarding any restrictive regulatory decisions adopted by the AREE.

CHAPTER IV
PROCEDURES FOR SUBMISSION OF AN APPLICATION FOR REGULARIZATION AND POST-REGULARIZATION THROUGH OPTIMIZED ANALYSIS PROCEDURE

Section I
Submission of regularization application through optimized analysis procedure

Art. 13. The application for regularization of a drug product, API, vaccine, or 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.

Art. 14. The applications for regularization submitted to ANVISA through optimized analysis procedure must be submitted in a specific addendum to the process or part(s) of the process whose optimization is requested, complementary to the previous article, with:

I - checklist, available in Annex II of this Normative Instruction, when related to drug products, vaccines or biological products;

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

III - instructional documentation issued by the AREE to which the regularization request was submitted and approved;

IV - proof of regularization granted by the AREE, in force at the moment of the application;

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

VI - report including the assessment of the instructional documentation provided to ANVISA, and also confirming that the drug product, vaccine or biological product and their active substances, object of the regularization application, have essential characteristics equivalent to the ones approved by the AREE.

§1º The applicant must identify the parts of the report referred to in item VI of the caption of this article that contain restricted information, as provided for in Law no. 12,527/2011.

§2º ANVISA, in Annex I, can waive the submission of documentation requested in item III of this article.

Art. 15. The instructional documentation required in this Normative Instruction can be sent to ANVISA,totally or partially, directly by the AREE when the applicant does not have access.

§1º The applicant is exclusively responsible for the actions described in the caption of this article.

§2º If the pertinent instructional documentation is not sent by the AREE, the documentation submitted shall be assessed, totally or partially, through ordinary analysis.

Section II
Submission of post-regularization application through optimized analysis procedure.

Art. 16. A post-regularization change approved by an AREE will be submitted to the optimized analysis procedure if it is demonstrated that the drug product has identical essential characteristics, or the same quality grade for the API.

Single paragraph. Any post-regularization change submitted to ANVISA, regardless of having been previously approved by ANVISA or not, and that turns out to be rejected by AREE, must be immediately communicated to ANVISA.

Art. 17. Post-regularization change application must be submitted with the documents listed below.

I - summary of deficiency letters sent by the AREE and respective response given in case of post-regularization changes that do not have assessment reports available by the AREE;

II - commitments assumed with the AREE, if any;

III - instructional documentation proving that the post-regularization change was approved by the AREE.

§ 1º The application referred in this article must be submitted, additionally, with the information and documents required by the ordinary analysis procedure of post-regularization changes.

§ 2º The application described in this article will be submitted to verified analysis.

§ 3º The post-regularization changes classified as immediate implementation maintain their situations, and all regulatory requirements must be complied for implementation.

Art. 18. Post-regularization changes applications that are not of immediate implementation must be submitted within 6 (six) months after approval by the AREE.

Single paragraph. In the cases where the post-regularization change application is submitted after the deadline described in this article, the possibility of adoption of optimized analysis procedure is suspended.

CHAPTER V
FINAL PROVISIONS

Art. 19. The regularization or post-regularization change application submitted to ANVISA through ordinary analysis can, as long as it is eligible under the terms of this Normative Instruction, be reframed in the optimized analysis procedure.

§ 1º The request for change of the analysis procedure referred in this article must be submitted in a specific addendum, as long as it is submitted before the start of the analysis, and must include all documents and information provided in this normative for optimized analysis.

§ 2º Anvisa's offices responsible for technical analyses, when having access to documents and reports issued by the AREE, may choose to apply the optimized analysis procedure to assess applications at any time, recording the adoption of such approach in the respective process.

§ 3º Requests previously rejected by the Resolution - RDC nº 750/2022, can be resubmitted and reassessed based on the requirements established in this Normative Instruction.

Art. 20. A conditional approval shall be published referring to the post approval change application of quality of biological products and vaccines in the following conditions:

I - if there is the specific addendum provided for in this Normative Instruction approved by the responsable office;

II - if the period and period extension, established in Law no. 13,411/2016, are overdue;

III - if there is no manifestation by Anvisa within 90 (ninety) days, after the submission of the addendum provided for in item I of this Article.

§ 1º The provisions of this article do not apply to post approval change applications related to safety and efficacy analysis.

§ 2º The conditional approval referred to in this article can be automatically reversed, at any time, and in case of rejection of the post approval change.

Art. 21. The use of the optimized analysis procedure established in this Normative Instruction does not prevent ANVISA from proceeding to reassessment, at any time, of the application through the ordinary analysis.

Art. 22. The decision regarding the regularization applications submitted through optimized analysis procedure is ANVISA's exclusive competence and is not linked to the decisions and conditions approved by the AREE.

Art. 23. Failure to comply with the provisions contained in this Normative Instruction constitutes sanitary infraction under the terms of Law n° 6.437/1977, without prejudice to applicable civil, administrative, and criminal liabilities.

Art. 24. The optimized analysis applications submitted during the validity of Resolution - RDC nº 750/2022, which are pending decision on the implementation of this Normative Instruction will be assessed according to the rules established in the mentioned Resolution.

Art. 25. This Normative Instruction comes into force on 1 April 2024.

ANTONIO BARRA TORRES

ANNEX I - Equivalent Foreign Regulatory Authorities (AREE) designated by ANVISA.

I - European Medicines Agency - EMA (centralized analysis processes), applicable to drug products, vaccines, and biological products;

II - Health Canada, applicable to drug products, vaccines, and biological products;

III - World Health Organization – WHO, applicable to API, drug products, vaccines and biological products;

IV - European Directorate for the Quality of Medicines & HealthCare - EDQM, applicable to API. Presentation of instructional documentation dispensed under the terms of § 2nd of art. 14 of this Normative Instruction;

V - Swiss Agency for Therapeutic Products - Swissmedic, applicable to drugs products, vaccines, and biological products;

VI - Medicines and Healthcare products Regulatory Agency - MHRA, United Kingdom: applicable to drug products, vaccines, and biological products;

VII - US Food and Drug Administration - FDA: applicable to drug products, vaccines, and biological products; and

VIII - Therapeutic Goods Administration (TGA) - Australia: applicable to drugs products, vaccines, and biological products.

ANNEX II - Checklist for assessment of qualification of petitions for registration of drugs, vaccines, biological products and their active substances through optimized analysis procedure.

GENERAL INFORMATION	
Registration process number:	
Number of the record(s) that pleads for the application of optimized analysis procedure:	
Subject(s) of the petition(s):	
Product name:	
Inform the regulatory authority(ies) that approved the request for regularization to be submitted:	
Parts of the dossier to which optimized analysis is requested: Note: Fill in exclusively the section of the checklist below belonging to the parts of the dossier where the use of optimized analysis is requested.	Safety Efficacy Quality

CRITERION	**CHECKLIST**
Administrative information (applicable to all processes)	
General	
Is the instructional documentation submitted from an Equivalent Foreign Regulatory Authority (AREE) designated by ANVISA?	**Yes.** Inform the name of the AREE chosen as reference and approval date: AREE name:_____ Approval date: _____ **No.** Request not eligible for the optimized analysis procedure.
Is there complementary information added to the request issued by another AREE?	No. Informational item Yes. Inform the name of the AREE chosen as reference and approval date: AREE name:_____ Approval date: _____
Does the registration/regularization requester belong to the same corporate group as the holder of registration/regularization approved by the AREE?	**Yes.** Request is eligible for the optimized analysis procedure. **No.** Necessary to attach an authorization letter by the holder of the registration/regularization confirming that the requester is acting according to the rights derived from the holder of the registration/regularization and that the holder agrees with the application of the procedure in Brazil.
Does the dossier meet the following eligibility criteria?	**Yes.** Eligible for the optimized analysis procedure.

1 – The instructional documentation issued by the AREE refers to assessment for definitive approval for marketing the drug, vaccine, or biological product, that is, it was not approved on an interim basis, or conditionally. 2 - The instructional documentation issued by the AREE is complete, in Portuguese, English, or Spanish. 3 – A request for approval for marketing the drug, vaccine, or biological product object of this request was not denied, rejected, refused, or withdrawn in any country of the AREE.	**Only item 3 is not met.** Inform the countries and attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure. **Item 1 or 2 is not met.** The request is not eligible for the optimized analysis procedure.
Was the request for registration or authorization for marketing the drug, vaccine, or biological product object of this petitioning rejected or is being marketed upon judicial decision in any country?	**No.** Eligible for the optimized analysis procedure. **Yes.** Inform the country and attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure. Country: _____
International alignment of guidelines	
Does the AREE instructional documentation mention or was prepared observing the guides published by ICH or WHO?	**Yes.** The request is eligible for the optimized analysis procedure **No.** Necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Does the AREE's instructional documentation mention or was prepared observing ICH or WHO non-clinical guidelines?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** Necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Does the AREE's instructional documentation mention or was prepared observing ICH or WHO efficacy and safety guidelines?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** Necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Does the report mention specific guideline or guide, distinct from ICH or WHO references?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** It ts necessary to attach clarification identifying or justifying the divergences across guidelines or guides adopted by

	the AREE and ICH or WHO guidelines. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Quality	
Characteristic of the drug, vaccine, or biological product object of this petitioning	
Does the API, drug, or biological product object of this petitioning present essential characteristics identical to those approved by the AREE and described in the AREE instructional documentation presented, regarding the criteria described below? 1 - Dosage; 2 - Concentration; 3 - Formulation (API or active substance and excipients); 4 - Manufacturers (starting material, intermediate, API or active substance, intermediate product, drug, vaccine, or biological products and packaging); 5 - Manufacturing process (active substance, intermediate product, drug, or biological product). 6 - Cell and viral banks, where applicable. 7 - Molecular characterization, where applicable. 8 - Specifications of release and stability (biological product and its active substances).	**Yes.** The request is eligible for the optimized analysis procedure. **No.** The request is not eligible for the optimized analysis procedure.
Was the generic drug/similar developed based on the reference drug chosen by ANVISA?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** The request is not eligible for the optimized analysis procedure. Not applicable. It is not a generic drug.
Additional manufacturing locations	
Are additional manufacturing locations (not included in the dossier sent to the AREE) indicated in this submission to ANVISA?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** Necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure. Information on the plant must

	be presented and will be subjected to ordinary assessment.
Is the additional location destined only for stages of labeling, secondary packaging, or release of batches for distribution?	**Not applicable.** There are no additional manufacturing locations. **Yes.** The request is eligible for the optimized analysis procedure. **No.** Other stages are performed in the additional locations. It is necessary to attach clarification describing the additional stages. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure. If eligible, ordinary analysis will be applied to the whole quality documentation related to the additional plant.
Were the validation data, including analyses of batches, for additional location provided?	**Not applicable.** There are no additional manufacturing locations. **Yes.** The request is eligible for the optimized analysis procedure. **No.** The request is not eligible for the optimized analysis procedure. **Note:** additional assessment may be necessary.
Good Manufacturing Practices (GMP)	
Do all manufacturing locations indicated have valid Good Manufacturing Practices Certificate (GMPC) issued by ANVISA?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** The request is eligible for the optimized analysis procedure as long as the inspection(s) has already been scheduled with ANVISA. **Not applicable.** GMPC issued by ANVISA is not required by the legislation in force. It is necessary to attach documentation issued by the AREE proving the regularity of the production plant with regard to Good Manufacturing Practices with the AREE.
Stability, period of validity, and packaging	
Were the stability studies assessed by the AREE for granting of period of validity conducted according to the climatic zone (IVb)?	**Yes.** The request is eligible for the optimized analysis procedure. **No,** because the drug, vaccine or biological product object of the request must not be stored at room temperature (e.g.. hospital use or refrigerated). The request is eligible for the optimized analysis procedure.

	No, but stability studies zone IVb are being sent. The request is eligible for the optimized analysis procedure. **No.** The request is not eligible for the optimized analysis procedure.
Are the period of validity proposed, the period of validity in use, and storage conditions identical to those accepted by the AREE?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** It is necessary to attach clarification about the specific period of validity proposed. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Information on the API regularization	**Not applicable (check this option in case the product object of analysis does not have synthetic or semi synthetic API liable to regularization)**
Will the API regularization be conducted by optimized analysis procedure?	**Yes.** The holder of the DIFA must fill in Annex III and submit it in the API regularization process. **No.** Include in the drug registration process copy of the CADIFA (or file "Notification of CADIFA Process") and additional information.
Safety and efficacy	
Indications and instructions for use	
Are the therapeutic indications proposed equivalent to those approved by the AREE, including dosage, target population, route of administration, and conditions of use?	**No.** The request is not eligible for the optimized analysis procedure. **Yes.** Inform the hyperlink for access to the public AREE approval report, if available: _____
Are the indications proposed identical to the indications proposed to the reference drug or comparison product in Brazil?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** Necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure. **Not applicable.** It is not generic drug or biosimilar.
Leaflets	
Does the AREE instructional documentation provide safety and efficacy information required for the preparation of the national drug leaflet text, considering the requirements in RDC 47/2009?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** Clarification must be presented.

Clinical trials	**Not applicable (check this option in case clinical trials were conducted for the product object of analysis (ex. generic)**
Was the drug, biological product, or vaccine clinical trial or part of it conducted in Brazil?	**No.** **Yes.** Inform which trial phase was conducted
Are there smaller updates or main trials or support studies available that were not considered in the AREE approval supporting the indication proposed?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** It is necessary to provide details like annotations in the drug leaflet proposed with references to relevant documentation. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Is there any relevant additional information available regarding the benefit-risk ratio of the indication approved by the AREE (for example, additional Periodic Safety Update Report or long-term safety study available since the approval)?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** It is necessary to submit additional information. The request is eligible for the optimized analysis procedure. In case of post-approval change the optimized procedure is not applicable.
Were new clinical trials conducted or new clinical evidences obtained since the drug, vaccine, or biological product was assessed by the AREE?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Are there bridge studies designed for adequacy of the drug, vaccine, or biological product to the Brazilian population?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** Only quality aspects are eligible for the optimized analysis procedure.
Generic drugs	**NA (check this option in case the product object of analysis is not a generic drug)**
Was the reference drug used in comparability studies presented to the AREE a drug currently registered in Brazil?	**No.** Informational item **Yes.** Inform the registration number in Brazil. Registration number: _____
Did the dossier submitted to the AREE contain bioequivalence and bioavailabiliity data (biopharmaceuticals)?	**Yes.** Informational item **No.** It is necessary to attach clarification for not submitting the biopharmaceutical data to the AREE.
Is a reference drug registered in Brazil used for bioequivalence and bioavailability (biopharmaceuticals) studies?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** It is not eligible for the optimized analysis procedure. **Not applicable.** The product is liable to bio exemption according to national regulation in force. It is necessary to

	attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure. **Not applicable.** The reference drug considered by the AREE and the reference drug in Brazil are manufactured in a single location for global distribution. It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Biosimilars	**Not applicable (check this option in case the product object of analysis is not a biosimilar)**
Is the comparison product representative of the national product?	Yes. Inform the registration number in Brazil. Registration number: _____ No. Not eligible for the optimized analysis procedure.
Risk Management Plan (RMP)	**Not applicable (check this option in case a Risk Management Plan (RMP) is not required according to Brazilian regulation in force)**
Are any of the following documents being submitted? I – RMP approved by the AREE; II – Global/general RMP; or	**Yes.** List the documents' names. **No.** Not eligible for the optimized analysis procedure.
Is a specific RMP being submitted to Brazil?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Is a current RMP approved by the AREE being submitted?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Are there questions related to the risk management specific to the Brazilian scenario being submitted to ANVISA?	**No.** The request is eligible for the optimized analysis procedure. **Yes.** It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.

Is the risk management system proposed o Brazil equivalent to that approved by the AREE?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Does the AREE report include assessment of the RMP presented (current or previous version) and comments on the adequacy of the Summary of Safety Concerns?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Does the AREE report include assessment of an RMP, proposing a risk management system equivalent to the one proposed to Brazil (including equivalent pharmacovigilance and risk minimization activities, and considerations on the adequacy of the Summary of Safety Concerns)?	**Yes.** The request is eligible for the optimized analysis procedure. **No.** It is necessary to attach clarification. Subject to assessment, by ANVISA, of the eligibility for the optimized analysis procedure.
Conclusion	
Was any of the answers to the questions in this checklist checked indicating that the request is not eligible for the optimized analysis procedure?	Yes. The request is not eligible for the optimized analysis procedure. No.

Based on the above checklist, I formalize the submission of dossier for the optimized analysis procedure.

I am aware that ANVISA can, according to technical assessment of the information provided, adopt the ordinary analysis procedure.

I declare that the petitioning company is a legitimate part of the process of submission of request(s) for registration(s) with the AREE, and, consequently, to ANVISA.
While completing and signing this form, I authorize ANVISA, if necessary, to contact the AREE and share information related to my petitioning.
Date: __/__/____
Name: _____
Signature: _____

Annex III - checklist for for the assessment of eligibility for the optimized analysis procedure of CADIFA applications.

GENERAL INFORMATION

GENERAL INFORMATION	
API:	
Equivalent Foreign Regulatory Authority (AREE):	
CEP or CPQ number:	

Criteria	**Checklist**
General	
Was the submitted regulatory documentation issued by an equivalent EFRA designated by Anvisa?	☐ **No**. The application is not eligible for the temporary optimized analysis procedure. ☐ **Not Applicable**. Regulatory documentation is not mandatory for this EFRA (i.e. EDQM). Name of the EFRA: Date of approval: ☐ **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 AREE with Anvisa.
Does the AREE's regulatory documentation 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 censored.	☐ **Yes.** The application is eligible for the temporary optimized analysis procedure. ☐ **Not Applicable**. The regulatory documentation is not mandatory for this AREE (i.e. EDQM). Name of the AREE: Date of approval: ☐ **No**. The application is not eligible for the temporary optimized analysis procedure.

Criteria	Checklist
Was the application for regularization of the API object of this petition denied, rejected, refused, or withdrawn, or is it commercialized with a court order in any country?	☐ **No.** The application is eligible for the temporary optimized analysis procedure. ☐ **Yes**. Inform the country and details on the case: Subject to assessment by Anvisa of the eligibility for the temporary optimized analysis procedure.
Was there a withdrawal of application for marketing authorization for the medicinal product or biological product in any of the EFRAs designated by Anvisa?	☐ **No**. The application is eligible for the temporary optimized analysis procedure. ☐ **Yes**. Inform the AREE and attach clarifications. Subject to assessment by Anvisa of the eligibility for the temporary optimized analysis procedure. Country:
Active Pharmaceutical Ingredient Dossier (DIFA)	
Is the DIFA approved by an AREE?	☐ **No.** The application is not eligible for the temporary optimized analysis procedure. ☐ **Yes.** Inform the name of the AREE and the date of approval by the AREE. In addition, inform the Version of the DIFA submitted to the AREE. Name of the AREE: Date of approval: Version of the DIFA submitted to the AREE:
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 AREE.	☐ **Yes.** Inform the document version and its respective issuer. Document version: Issuer: ☐ **No**. The application is not eligible for the temporary optimized analysis procedure. ☐ **Not applicable.** The API temporary 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 AREE?	☐ **Yes.** The application is eligible for the temporary optimized analysis procedure. ☐ **No.** In case this option is checked, indicate on the list below the sections with distinct information, if any. For unchecked sections, present Comparative Table (Annex 8 of the CADIFA's Application Form), for assessment of the eligibility for the temporary optimized analysis procedure. Subject to assessment by Anvisa of the eligibility for the temporary optimized analysis procedure. If eligible, additional assessment may be carried out. 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) ☐ Impurities (3.2.S.3.2) 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)

Criteria	Checklist
	☐ Protocols and Post-submission Commitments (3.2.S.7.2) ☐ Stability Data and Reports (3.2.S.7.3)
Conclusion	
In any of the questions in this checklist, was an answer checked indicating the application is not eligible for the temporary optimized analysis procedure?	☐ **Yes.** The process is not eligible for the temporary optimized analysis procedure. ☐ **No.** Answer the next question
In any of the questions in this checklist, was an answer checked informing that an additional assessment may be carried out?	☐ **Yes.** Eligibility assessment depends on analysis of the documents attached to this checklist. ☐ **No.** The process is eligible for the temporary optimized analysis procedure.

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

I hereby declare that the API approved by the AREE 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. Specification and analytical methods of intermediate products;
6. Specification and analytical methods of APIs;
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 the Applicant is a legitimate party of the application with the AREE and, consequently, with Anvisa.

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

Date: __/__/____

Name:

Signature (DIFA Contact): _____

Name:

Signature (DIFA Holder Responsible Official/Legal Representative):
_____