Active Pharmaceutical Ingredients

Brazillian Health Regulatory Agency - ANVISA

Active Pharmaceutical Ingredients – Questions and Answers & Legislation

1st edition

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SUMMARY

1. INTRODUCTION

This document presents some of the frequently asked questions about active pharmaceutical ingredients market authorization in Brazil and some of the legislation related to APIs.

General doubts about the API marketing authorization process in Brazil, by companies without a corporate taxpayer-s ID (CNPJ), may be sent to coifa@anvisa.gov.br to help us improve this document.

Matters related to a specific application of an API market authorization dossier, for safety reasons, are to be sent by the Brazilian Applicant.

2. QUESTIONS AND ANSWERS

1 Who may apply for the market authorization of an ASMF/DMF in Brazil?
It is required for the legal entity making the submission to the regulatory agency to have a *National Register of Legal Entities number (CNPJ).* In other words, the company must have an office in Brazil. That said, the importer, the drug substance manufacturer or the drug product manufacturer may apply for the registration of the DMF.

2 Which API must be registered?
Please refer to IN 15/2009 e IN 03/2013.

3 Must the ASMFs/DMFs application be in Portuguese?
The application form is in Portuguese.
The "technical documentation" is accepted in English.

4 Where do I find some orientations about how to submit an application for API registration?
Please refer to RDC 57/2009 and IN 1/2015.

5 May I submit the documentation in the ICH's Common Technical Document (CTD) format for ASMFs/DMFs?
Yes. Anvisa hasn´t adopted the eCTD format, but since most of the information required by the RDC 57/2009 is similar to the information on the CTD, the applicant may submit the documentation in this format and include the additional information needed.
Obs.: It´s advisable to send the complete documents used in the eCTD, instead of extracting the information from each .pdf document.

6 Which CTD sections must be included in an ASMF/DMF?
Generally speaking, sections 3.2.S.1 to 3.2.S.7.
(In addition to the information required by the RDC 57/2009).

7 May I submit the documentation on a CD (compact disk) instead of paper?
Yes, please send the documentation in a searchable and indexed pdf file.

8 Where do I find some orientations about the stability studies?
Please refer to RDC 45/2012.

9 Does Anvisa issue Free Sale Certificates (Registration Certificate for Export) for active pharmaceutical ingredients (APIs)?
No, Anvisa doesn´t issue Free Sale Certificates for APIs.

10 Is there a figure as in FDA for a complete DMF in order to be submitted to the Brazilian Authority and make the customers make reference to it?
No, there isn´t. Each applicant must send the complete documentation for the API.

3. LEGISLATION

RESOLUTION – RDC No. 57, OF NOVEMBER 17th, 2009

Provides for the registration of active pharmaceutical ingredients (API) and takes other measures.

The National Health Regulatory Agency's Collegiate Directorate, in the use of the attributions granted to it by subparagraph IV of art. 11 of ANVISA's Regulation approved by Decree 3,029, of April 16th, 1999, and considering the provisions of subparagraph II and in § § 1st and 3rd of art. 54 of the Rules of Procedure approved pursuant to Attachment I of ANVISA's Ordinance no. 354, of August 11th, 2006, republished in the DOU of August 21st, 2006, in the meeting held on April 14th, 2000,

whereas health is the right of all and duty of the State, guaranteed upon social and economic policies intended to decrease the risk of disease and other grievances and the universal and equal access to the actions and services for its promotion, protection and recovery, pursuant to art. 196 of the Constitution of the Federative Republic of Brazil, of October 05th, 1988;

whereas the healthcare actions and services are of public relevance, pursuant to art. 197 of the Constitution, being the Public Power responsible for providing, pursuant to the law, for its regulation, inspection and control;

whereas the provisions contained in Law no. 6,360, of September 23rd, 1976, and in Decree no. 79,094, of January 05th, 1977, concerning the health regulatory system the medicines, drugs, the pharmaceutical ingredients, correlates and other products are subject to;

whereas Law no. 6,437, of August 20th, 1977, which provides for the infringements to the federal health legislations and establishes the respective penalties;

whereas health is an essential right of the human being, being that the State must provide the indispensable conditions for its full exercise, as provided for by art. 2nd of the Organic Health Law (OHL), Law no. 8,080, of September 19th, 1990;

whereas Anvisa's institutional purpose of promoting the population health protection and its duty of coordinating the National Health Regulatory System, as established in art. 6th and in subparagraphs I, III and XXII of art. 7th of Law no. 9,782, of January 26th, 1999;

whereas the directives, priorities and responsibilities established in the National Drug Policy, established by Ordinance no. 3,916/MS/GM, of October 30th, 1998, intended to guarantee safety and quality conditions for drugs consumed in the country, promote the rational use and access of the population to those considered as essential;

whereas the provisions contained in Resolution no. 338, of May 06th, 2004, of the National Health Council, which approves the National Pharmaceutical Assistance Policy, defining its principles and strategic axes, among which the qualification of the existing pharmaceutical assistance services and the construction of a Health Regulatory Policy which guarantees the access of the population to services and products, safe, efficient and with quality, are included;

whereas Resolution RDC no. 249, of September 13th, 2005, which provides for the Good Manufacturing Practices of Intermediate Products and Active Pharmaceutical Ingredients;

whereas the Active Pharmaceutical Ingredients Program created by means of Resolution RDC no. 250, of September 13th, 2005;

whereas Resolution – RDC no. 30, of May 15th, 2008, which provides for the obligation of registering active pharmaceutical ingredients in Anvisa's scope;

whereas Ordinance no. 978, of May 16th, 2008, which provides for the list of strategic products, in the scope of the Brazilian Unified Health System, with the purpose of collaborating with the development of the Industrial Health Complex and establishes the Commission for Reviewing and Updating the referred list;

whereas the need to regulation the registration of active pharmaceutical ingredients in Brazil, so as to improve the quality control of such products in the country and the health requirements guaranteeing the efficacy and safety of drugs,

adopted following Collegiate Directorate Resolution and I, Director-President, determine its publication:

Art. 1st Approving the Technical Regulation for the registration of Active Pharmaceutical Ingredients (APIs) in Brazil, pursuant to the ATTACHMENT to this Resolution.

Art. 2nd The active pharmaceutical ingredients, including the imported ones, after the adequacy period addressed by art. 3rd of this regulation, cannot be industrialized, exposed to sale or marketed in the country before they are registered by Anvisa, except the active pharmaceutical ingredient which will be used for scientific or technological research, as well as for the research and development of formulations.

§ 1st The registration of active pharmaceutical ingredients exclusively intended for export will be optional.

§2nd The registration referred to in the caput of this article will be valid for 05 (five) years and may be revalidated by equal and successive periods, maintaining the initial registration number.

§ 3rd The registration revalidation must be required in the first semester of the last year of the five-year validity period, from the date the registration is published, being considered as automatically revalidated, regardless of decision, if this has not been granted until its expiration date.

§ 4th It will be declared the registration expiration of the product for which the revalidation has not been requested within the period referred in § 3rd of this article.

§ 5th The registration of active pharmaceutical ingredients addressed by this resolution will not be granted when the conditions, requirements and procedures provided for in this regulation are not met.

§ 6th Anvisa may, on an emergency or temporary basis, exempt active pharmaceutical ingredients exclusively intended for the production of drugs to be used in public healthcare programs by the Ministry of Health and its associated entities from being registered.

I – The exemption from registration of the active pharmaceutical ingredients addressed by paragraph 5th, will be under exclusive authorization by ANVISA's Collegiate Directorate, in a formal and public act subscribed by the Director President.

Art. 3rd The companies established in the country manufacturing or importing active pharmaceutical ingredients must adjust their activities to the provisions of this Resolution, according to the chronogram approved by the Collegiate Directorate, also containing the list of substances ordered and classified according to the following adequacy priority criteria:

I – Low Therapeutic Index Drug Substance.

II – Drug substance produced in the country.

III – Drug substances included in the strategic ingredients list defined by the Ministry of Health.

IV- Drug substances intended for the production of drugs used in Strategic Programs defined by the Ministry of Health.

V – Drug substances intended for the production of drugs described in the National List of Essential Drugs (Rename).

VI – Drug substances intended for the production of drugs for dispensing in exceptional character.

VII – Drug substances used in the public production of drugs for neglected diseases, as defined by the Ministry of Health.

VIII – Drug substances used in the production of drugs belonging to the therapeutic categories of the antineoplastics, antibiotics and immunosuppressors.

IX – Drug substances used for the production of generic drugs.

X – Drug substances used for the production of drugs intended for the basic healthcare.

Sole paragraph. The publication of the chronogram addressed by this article will be conducted in regulatory act by Anvisa's Collegiate Directorate, in which the period for adequacy will be established.

Art. 4th The active pharmaceutical ingredients present in the imported drugs composition, whether under the form of semi-elaborated or finished product, must be registered as provided for in this standard.

Art. 5th The failure to comply with the provisions contained in this Resolution and in the Regulation approved by it constitutes a health violation, pursuant to Law no. 6,437, of August 20th, 1977, without prejudice to the applicable civil, administrative and penal liabilities.

Art. 6th This Resolution comes into force on the date it is published.

DIRCEU RAPOSO DE MELLO

ATTACHMENT

TECHNICAL REGULATION FOR THE REGISTRATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

1. OBJECTIVE:

Establishing the requirements for the registration of active pharmaceutical ingredients in order to guarantee the quality and allow their use in the elaboration of pharmaceutical products in the country.

2. SCOPE:

This regulation applies to companies established in the country manufacturing or importing active pharmaceutical ingredients and refers to all the active pharmaceutical ingredients, national or imported.

2.1. This Resolution applies to synthetic active pharmaceutical ingredients used in drug manufacture.

I – The registration of the APIs used in herbal drugs, dynamized and biological products, including sera and vaccines are separately discussed in specific regulations.

3. DEFINITIONS:

For the purposes of this Technical Regulation, the following definitions are adopted:

3.1 Brazilian Non-Proprietary Name (BNN) - Name of the drug product or pharmacologically active substance approved by the Federal Body responsible for Health Regulatory.

3.2 International Non-Proprietary Name (INN) - Name of the drug product or pharmacologically active substance approved by the World Health Organization.

3.3 Specification - The detailed description of the requirements to which the products or materials used or obtained during manufacture must meet. It serves as the basis for quality evaluation.

3.4 Manufacture - All the operations including the purchase of materials, production, quality control, release, storage, shipment of finished products and related controls.

3.5 Impurity – Any undesirable component, present in the intermediate or in the active pharmaceutical ingredient.

3.6 Active Pharmaceutical Ingredient (API) – Also called drug product, or simply active substance, is the pharmacologically active component intended for use in drugs.

3.7 Batch - Specific amount of product obtained by means of a process or a series of processes, so that it is homogeneous, within the specified limits. In case of continuous production, a batch may correspond to a defined fraction of production, determined by a pre-determined amount of mass or by the produced amount at a fixed time interval.

3.8 Raw Material - Active or inactive substances used for the manufacture of ingredients, even if they remain unchanged, are changed, or eliminated during the manufacturing process.

3.9 Material – A generically used term which includes raw materials, intermediate auxiliary materials, active pharmaceutical ingredients, packaging and labeling materials.

3.10 Packaging material – Any form of packaging, intended to protect and maintain the intermediates and active pharmaceutical ingredients, including the labeling material.

3.11 Starting Material - Chemical and/or biological material which originates the intermediate product or the pharmaceutical product.

3.12 Starting Material - Chemical substance used in the production of an active pharmaceutical ingredient, which is incorporated in it as an important structural element. The starting material has well defined denomination, chemical structure, properties and physical-chemical characteristics and impurity profile.

3.13. Batch Number - Any combination of numbers or letters through which it is possible to trace the full manufacturing history of the batch and it movement in the market.

3.14 Primary reference standard – Substance for which the high purity and authenticity degree were demonstrated by means of analytical tests.

3.15 Secondary reference standard - Substance of established quality and purity, after comparison with a primary reference standard.

3.16 Polymorphism – The property of certain substances of presenting more than one crystalline form.

3.17 Expiration date – Time during which the product can be used, characterized as the useful life period and based on specific stability studies.

3.19 Process - Set of single operations, following techniques, standards and specifications.

3.20 Production of Active Pharmaceutical Ingredient – Set of operations involved in the preparation of intermediate product or active pharmaceutical ingredient, from the receipt of the materials from the warehouse, passing through processing and packaging.

3.21 Finished product: Product which has been through all the production steps, including labeling and packaging.
3.22 – Chiral molecules – Molecules of identical chemical composition, but for which the specular images are not overlapping.
3.23 Label - Printed, lithographed, painted, heat-printed, pressure-printed or self-adhesive identification, directly applied to the containers, packages, cases or any external or internal package protective device, which cannot be removed or changed during the product use and during its transportation or storage.
3.24 Solvent – Organic or inorganic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of pharmaceutical ingredients.
3.25 Validation - Documented act which confirms that any procedure, process, equipment, material, operation or system really takes to the expected results.
3.26 CAS Number – Registration number at the Chemical Abstract Service (CAS). It is a numeric identifier which contains a maximum of 09 digits divided into 3 parts. Each registration number at CAS is single, designating only one substance, without chemical meaning and is a link to a rich information source about a specific chemical substance.
3.27 Intermediate – Partially processed product which must be submitted to more manufacturing steps before the active pharmaceutical ingredient is obtained.
3.28 Auxiliary materials - Materials used as auxiliaries in the production of an intermediate or active pharmaceutical ingredient, which do not participate in the chemical or biological reaction itself.
3.29 Enantiomeric purity – An excess measure, normally expressed in percentage terms, of the enantiomer of interest over the total of the enantiomers mixture.
3.30 Technical Report: Conclusive document presented by the company, containing information which characterize the product and which comply with the health authority requirements so that it can render a decision about the registration.
4. REGISTRATION DOCUMENTATION:
By the time the active pharmaceutical ingredient registration application is submitted, the company must file a single process, composed of the following documentation:
4.1. Duly completed application forms;
4.2. Original copy of the proof of payment of the health regulatory inspection fee or the exemption form, when applicable.
4.3. Copy of the company's updated Operating License (Health Permit).
4.4. Copy of the company's Operating Authorization and the Special Operating Authorization, when applicable, published in the Official Gazette of the Federal Executive.
4.5. Copy of the updated Good Manufacturing Practice and Control of Pharmaceutical Ingredients Certification, issued by Anvisa or proof of the Technical Operational Conditions issued by the local health authority or protocol requesting the inspection by the health authority, provided that it had achieved satisfactory status on its last inspection.
4.6. For imported APIs, submit copy of the updated Good Manufacturing Practice and Control of Pharmaceutical Ingredients Certification, issued by Anvisa or protocol requesting the inspection by Anvisa, provided that it had achieved satisfactory status on its last inspection.
4.7. Copy of the Certificate of Technical Responsibility in effect, of the company requesting the registration, issued by the Regional Council of Chemistry or Pharmacy.
4.8. Proof of duly completing the registration form of the API at ANVISA's website.
4.9. Documentation required by the current legislation on the Transmissible Spongiform Encephalopathy (TSE) control.
4.10. Technical report containing the information described in item 5, below.
All the documentation in item 5 must be submitted in letterhead of the active pharmaceutical ingredient manufacturer in Portuguese language (see Resolution approved by DICOL).
The drug product manufacturer(s) may send directly to ANVISA the documentation outlined in this regulation, duly identified with the process number it relates to.
5. TECHNICAL INFORMATION ON THE ACTIVE PHARMACEUTICAL INGREDIENT:
The registration documentation must also contain the following information:
5.1. General information:
a) Nomenclature: Brazilian Non-Proprietary Name or, if absent, the International Non-Proprietary Name.
b) CAS no.
C) Chemical name
d) Synonyms with complete reference

e) Molecular and structural formulas
f) Molecular weight
g) Physical form
h) Melting or boiling point
i) Solubility
j) Loss on drying
k) Physical characteristics (crystalline, amorphous, particle size, solvation, etc.)
l) pka and pH
m) Preservation measures
n) Organoleptic properties

5.2. API manufacturing process:

a) Manufacturer(s): name, full address, company responsible for each manufacturing process step and quality control (including contracted companies, third-parties).

b) Description of the production process, including materials, equipment and operating conditions (for example, temperature, pressure, pH, time ranges, stirring speed, etc.); and of the in-process controls.

c) Identification of the critical steps including the respective tests and acceptance criteria.

d) Production process flowchart indicating the formation of intermediates and possible impurities, including the clarification of the respective chemical structures.

e) Indication of the raw materials, solvents, catalysts, etc…

f) Indicate the production scale and yield.

g) Specifications of the raw materials and packaging materials.

5.2.1. Characterization:

Physicochemical tests allowing elucidation of the API structure:

a) Analyses of an industrial batch evidencing the functional groups, the chemical structure and the molecular formula expected for the API.

b) Possible Isomers.

c) Polymorphism, describing the characteristics of the polymorph used and of others related to the active pharmaceutical ingredient.

5.2.2. Impurity profile:

a) Description of the potential impurities, resulting from the synthesis, with a brief description and indicating the origin.

b) Organic Impurities (of the process and related substances): raw materials (starting), related products, intermediate products, degradation products, reagents and catalysts.

c) Inorganic Impurities: reagents and catalysts, heavy metals, inorganic salts.

d) Residual solvents.

5.3. Quality Control of the API:

5.3.1 Specifications
b) Appearance
c) Identification
d) Assay
e) Impurities (organic, inorganic and residual solvents)
f) Physicochemical properties (pH, melting point, etc.).
g) Particle size distribution.

h) Polymorphism, including the adopted analytical methodology and results of the tests intended to determine the probable polymorphs of the ingredient.

i) For chiral ingredients, data on the stereoisomers content.
j) Water determination
k) Microbiological limits: sterility, endotoxins (if applicable).
l) Specific optical rotation (if applicable)

5.3.2 Copy of the quality control report of three produced batches, identifying the API, the batch number, the reference values and the conducted tests results.

5.3.3 Description of the analytical methodology:

Validation of analytical methodology according to the current specific technical regulation for the validation of analytical and bioanalytical methods when the pharmacopeial methodology is not used.

In case of pharmacopeial methodology, the company must submit the method covalidation.

5.4 Packaging Material: description and specification of the primary packaging.

5.5 Stability and Photostability Report

The stability and photostability studies must be conducted in compliance with the specific technical regulation in effect in Brazil.
6. DOCUMENTATION FOR REGISTRATION RENEWAL:
For the renewal of active pharmaceutical ingredients registration, the company must submit the following documentation:
6.1. Duly completed application forms;
6.2. Original copy of the proof of payment of the health regulatory inspection fee or the exemption form, when applicable.
6.3. Copy of the Good Manufacturing Practice and Control Certification (CGMPC) issued by ANVISA for the active pharmaceutical ingredient object of registration, or copy of the inspection request protocol for the purposes of issuing the CGMPC, provided that it was satisfactory in the last inspection.
6.4. In case of ingredients exclusively registered for the purposes of export, according to this regulation, the proof of export must be submitted.
6.5. Listing of all the post-registration amendments and/or inclusions occurred during the last validity period of the product registration.
6.6. Conclusive results of long term stability studies, according to specific guide defined by Anvisa.

RESOLUTION – RDC No. 45, OF AUGUST 9th, 2012

Provides on the conduction of stability testing on active pharmaceutical ingredients.

The Collegiate Board of Directors of the Brazilian Health Surveillance Agency, in the use of the attributions vested in it under Article 15, items III and IV of Law no. 9,782, dated 26 January 1999, item II, and Paragraphs 1 and 3 of Article 54 of the Internal Regulation approved by Annex I of the Anvisa Decree no. 354 dated 11 August 2006, republished on the D.O.U. of 21 August 2006, and its updates, considering the provisions of items III of Article 2, III and IV of Article 7 of Law no. 9,782 of 1999, and the Program to Improve the Agency's Regulation Process, created by Anvisa Decree no. 422, dated 16 April 2008, in a meeting held on 27 July 2012, adopts the following Collegiate Board Resolution and I, Director-President, determine its publication:
Article 1. The Technical Regulation that establishes the minimum requirements for the conduction of stability testing on active pharmaceutical ingredients (APIs) is approved, in the terms of this Resolution.

CHAPTER I
INITIAL PROVISIONS
Article 1. This Resolution approves the Technical Regulation for the conduction of stability testing on APIs in order to predict, determine, or follow their re-test period or their shelf life.
Section I
Scope
Article 2. The manufacturers of APIs should follow the directives established in this Resolution.
Section II
Definitions
Article 3. For the purposes of this Resolution, the following definitions are adopted:
I – Re-test date – Date established by the API manufacturer, based on stability testing, after which the material should be re-tested to ensure that it is still adequate for immediate use, in accordance with stability tests defined by the API manufacturer, keeping the pre-established storage conditions.
II – Package – Casing, recipient, or any form of wrapping, removable or not, designed to cover, package, pack, protect, or keep, specifically or not, active pharmaceutical ingredients.

III – Primary package – Casing in direct contact with the API, which may be a recipient, wrapping, or any other form of protection, removable or not, designed to pack or keep, cover or package APIs.
IV – Accelerated stability testing – Test designed to accelerate possible chemical degradation and/ or physical alterations of APIs by using exaggerated storage conditions. The data obtained from these studies, inaddition to long term stability studies, may be used to assess longer term chemical and physical effects at non-accelerated conditions, and to assess the impact of short exposures in conditions other than those established on the API label.
V – Long term stability testing – Test designed to verify physical, chemical, biological, and microbiological characteristics of an API and, as an alternative, after the re-test date or the shelf life. The results are used to establish or confirm the re-test date or the shelf life, and to recommend storage conditions.
VI – Impurity – Any undesired component present in the intermediary product or in the API.
VII – Active Pharmaceutical Ingredient – API – Any substance introduced in the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient, and may have a pharmacological activity or other direct effect on the diagnosis, cure, treatment, or prevention of a disease, and it also may affect the human body's structure and operation.
VIII – Intermediate product – Substance that suffers molecular alteration or purification, obtained during the processing phases before becoming an active pharmaceutical ingredient.
IX – Batch – A specific quantity of active pharmaceutical ingredient obtained from a process or series of processes, in order to be homogeneous, within the limits established. In the case of continuous production, a batch may correspond to a defined fraction of production. The batch size may also be defined by a fixed quantity or by a quantity produced in a fixed period of time.
X – Pilot scale batch – An API batch produced by a process equivalent to the one of industrial production batches.
XI – Shelf life or expiration date – Period of time during which the API may be used, characterized as shelf life, based on specific stability testing, and maintaining the storage and transportation conditions established.
XII – Degradation/ Decomposition product – A molecule resulting from a chemical alteration occurred in the intermediate product or API due to the action of time and/ or the action of external agents, such as light, temperature, pH, water, or by the reaction to an excipient and/ or to the primary package.
XIII – Label – Printed, lithographed, painted, fire-engraved, pressure-engraved, or self-adhesive identification applied directly on recipients, packages, casings, or any external or internal package protector, which cannot be removed or altered during the API use and during its transportation or storage.
XIV – Forced degradation testing – Tests carried out to assess the intrinsic stability of the API as part of the development strategy, executed under more severe conditions than the ones used in the accelerated stability testing.
XV – Confirmatory stability testing – Tests carried out to define the conditions used in manipulating, packaging, and labeling the API.
XVI –Stability indicating method – Validated quantitative analytical methods designed to assess stability samples, able to detect alterations in the physical, chemical, or microbiological properties of a substance over time. Specific methods capable of measuring accurately the concentration of the API, degradation products, and other components of interest, without interference.

CHAPTER II
ON THE TECHNICAL REGULATION
Section I
General Considerations

Article 4. The re-test date or shelf life of the active pharmaceutical ingredient should be determined from a long term stability testing, according to the parameters defined in this Resolution.

Article 5. The re-test date or shelf life should be included on the label.

Article 6. The batches to be sampled should be representative of the manufacturing process, in both pilot and industrial scales.

Article 7. It is possible to establish a provisional re-test date or shelf life of a maximum of 24 (twenty-four) months with minimum results from six months of accelerated testing or twelve months of a long term testing.

Article 8. The stability of an active pharmaceutical ingredient should be determined before its commercialization and repeated after any significant alterations in the production processes.

Sole paragraph. Significant changes are those related to the alteration in the re-test date or shelf life, in conservation care, in the synthesis route, in the venue and production process of an active pharmaceutical ingredient.

Article 9. An expiration date must be established for labile active pharmaceutical ingredients and certain antibiotics.

Article 10. The analytical methods used in the stability testing should be validated and stability indicating.

Article 11. The stability testing for imported active pharmaceutical ingredients may be carried out abroad, in accordance with the parameters defined in this Resolution.

Section II

Batch selection

Article 12. The re-test date or the expiration date of the active pharmaceutical ingredient may be based on the stability testing of the pilot-scale batches.

Sole paragraph. The quality of the batches used in the stability testing should be equivalent to the industrial batch.

Article 13. The accelerated and the long term term stability testing should be carried out with at least three batches of active pharmaceutical ingredients.

Section III

Packaging and labeling

Article 14. The samples destined to the active pharmaceutical ingredient ingredient stability testing should be put in recipients with the same chemical composition and physical characteristics of the marketing package.

Article 15. The label and secondary package materials should not interfere in the quality of the active pharmaceuticalingredient, and should guarantee adequate protection against external influences and eventual contaminations.

Article 16. The storage recommendations should be included on the labels after the active pharmaceutical ingredient stability is assessed in the conditions provided for in this Resolution.

Paragraph 1. Whenever necessary, additional information should be included, such as “protect from light”, “keep in a dry place”, among others.

Paragraph 2. Terms such as “environment condition” or “environment temperature” should be avoided.

Paragraph 3. Temperature intervals should be supplied, particularly for the active pharmaceutical ingredient that cannot be frozen, when applicable.

Article 17. The labels must include the action to be taken in case of freezing for the active pharmaceutical ingredient that will be stored in refrigerators (2 - 8ºC).

Section IV

Specifications

Article 18. The protocol of the stability testing should consider physical, chemical, physical-chemical, biological, and microbiological assessments, when applicable.

Sole paragraph. The qualitative and quantitative presence or formation of by-products and/or degradation products should also be assessed, using an adequate and validated methodology.

Section V

Testing Frequency

Article 19. The tests related to the accelerated stability testing should be carried out in 0 (zero), 3 (three), and 6 (six) months and should includeassay of the active pharmaceuticalingredient, quantification of the degradation products and, when applicable, identification of the degradation products.

Sole paragraph. The other tests may be carried out only at the end of the 6 (six) months, taking the 0 (zero) moment as reference.

Article 20. The tests related to the long term term studies should be carried out in 0 (zero), 3 (three), and 6 (six), 9 (nine), 12 (twelve), 18 (eighteen), and 24 (twenty-four) months and should includeassay of the active pharmaceuticalingredient, quantification of the degradation products and, when applicable, identification of thedegradation products.

Paragraph 1. The testing carried out should be presented at the end of the required re-test date or period of validity, taking the zero moment as reference for the other tests.

Paragraph 2. For the long term testing, the samples should be assessed at least in the periods established in the caption of this article, and annually after the second year until the re-test date or intended expiration date, and all specific stability assessment testing described in the approved protocol should be carried out.

Article 21. The zero moment should be defined in the stability testing protocol.

Section VI

Storage Conditions

Article 22. The climate condition to carry out the long term term stability testings are:

I – For active pharmaceutical ingredients with storage conditions of up to 30ºC, the tests should be carried out at 30 ºC ± 2 ºC / 75% UR ± 5% UR.

II – For active pharmaceutical ingredients with storage conditions of 2 ºC to 8 ºC, the studies should be carried out at 5ºC ± 3 ºC.

III – For active pharmaceutical ingredients with storage conditions of -15 ºC to -25 ºC, the long term tests should be carried out at -20 ºC ± 5 ºC.

IV – Active pharmaceutical ingredients with storage conditions below -20 ºC should be dealt with on an individual basis.

Article 23. The climate conditions to carry out the accelerated stability tests are of 40 ºC ± 2 ºC / 75% UR ± 5% UR for active pharmaceutical ingredients with storage conditions of up to 30 ºC.

Sole paragraph. The accelerated stability testing should be carried out at 25 ºC ± 2 ºC / 60% UR ± 5% UR for active pharmaceutical ingredients with storage conditions of 2ºC to 8ºC.

Article 24. If significant changes occur in the results obtained in the accelerated testing conditions, the re-test period or expiration date should be based on the long term tests.

Article 25. If the active pharmaceutical ingredients with storage condition of 2ºC to 8ºC yield results out of specification in the first 3 (three) months of the accelerated testing, the effect of variations should be assessed in short periods, out of the recommended storage condition, for example, during expedition or handling.

Paragraph 1. The assessment referred to in the caption of this article may be based, if appropriate, on additional tests carried out in a single batch of the active pharmaceutical ingredient for a period shorter than 3 (three) months, performing tests more frequently than the usual.

Paragraph 2. It is not necessary to continue the testing up to 6 (six) months.

Article 26. The expiration date or re-test date shall be based only on the long term tests for active pharmaceutical ingredients with storage condition of - 15 ºC to - 25 ºC.

Sole paragraph. Tests should be carried out at least on a batch at a higher temperature (e.g. 5 ºC ± 3 ºC or 25 ºC ± 2 ºC), for an adequate period of time, in order to determine the effect of short intervals of the material's permanence out of the storage conditions described on the label, as occurs, for example, during handling or transportation.

Article 27. The real storage temperature and humidity should be monitored during the stability testing.

Paragraph 1. Small variations due to opening doors are inevitable.

Paragraph 2. The effect of variations due to equipment failure should be followed by the person responsible, and its impact should be recorded and assessed in the stability testing.

Article 28. The procedure to be adopted in case of freezing should be provided by the manufacturer, if such freezing is critical for the active pharmaceutical ingredient stored in a refrigerator (2 °C - 8 ºC).

Article 29. The stability testing may be carried out considering only the temperature parameter for the active pharmaceutical ingredient stored in a package that is confirmedly impermeable to humidity.

Section VII

Follow up Tests

Article 30. The follow up tests should be carried out in the same climate conditions as the long term test's, provided for in this Resolution.

Article 31. A documented program should be implemented to monitor the stability characteristics of the active pharmaceutical ingredients.

Sole paragraph. The results should be used to confirm the proposed storage conditions, re-test date or expiration date.

Article 32. The follow up test may only be carried out if the active pharmaceutical ingredient does not suffer any significant alterations after the conclusion of the long term stability test.

Sole paragraph. If there is a significant alteration in the active pharmaceutical ingredient, a new stability test should be carried out, as provided for in this Resolution.

Article 33. The first three commercial production batches should be included in the stability monitoring program in order to confirm the re-test date or the validity period.

Sole paragraph. When the data from previous tests show that the active pharmaceutical ingredient is stable for at least 2 (two) years, less than 3 (three) batches may be used.

Article 34. At least one batch per year of active pharmaceutical ingredient produced should be added to the stability follow up test and tested in order to confirm stability, except if no batch has been produced that year.

Article 35. The follow up test should include all tests of the stability testing protocol.

Section VIII
Tests of Forced Degradation

Article 36. The forced degradation tests on the active pharmaceutical ingredients help to identify its probable degradation products and the analytical procedure to be adopted in the stability study, and the nature of tests depends on the type of molecule to be tested.

Sole paragraph. The testing protocol must establish which tests are pertinent to the provisions in the caption of this article.

Article 37. The tests may be carried out on only one batch of the active pharmaceutical ingredient, and should include the effects of temperature, humidity, oxidation, light, and susceptibility to hydrolysis on a wide range of pH values.

Sole paragraph. If any of the tests mentioned is not carried out, such absence should be technically justified.

Article 38. The analysis of the degradation products yielded in the degradation tests may be used to establish the degradation route and to develop the validation of the analytical methods.

Sole paragraph. It may not be necessary to assess specifically some degradation products, as long as it is confirmed that these are not formed under the conditions of accelerated and long term stability.

Article 39. Synthesis impurities that are not degradation products do not need to be described in the stability testing, but there must be an assurance that they do not interfere in the identification of degradation products.

Section IX
Photostability Testing

Article 40. Photostability testing should be carried out in order to show that exposition to light does not result in significant alterations in the active pharmaceutical ingredient.

Paragraph 1. Photostability testing may be performed with one batch of the active pharmaceutical ingredient.

Paragraph 2. The absence of photostability testing must be technically justified, with scientific evidence that the active pharmaceutical ingredient does not suffer degradation in the presence of light.

Article 41. The photostability testing must comprise two parts: forced degradation and confirmation test.

Article 42. In the forced degradation tests, the samples must be placed into chemically inert and transparent recipients.

Article 43. In the forced degradation tests, various exposure conditions may be used, depending on the substance's photosensitivity and the intensity of the source used.

Article 44. For development and validation purposes, it is appropriate to limit the exposure of the active pharmaceutical ingredient and finish the tests before excessive decomposition.

Paragraph 1. The tests may be finished after an appropriate level of exposure for photostable materials.

Paragraph 2. The exposure levels used by the company must be justified.

Article 45. Under forced conditions, decomposition products may be observed, which are unlikely to be formed under the conditions used in the confirmation tests.

Sole paragraph. There is no need to assess the degradation products, if verified they are not formed in the confirmation tests.

Article 46. If the active pharmaceutical ingredient is tested during the development phase, the photostability characteristics should be confirmed in a batch representing the production.

Sole paragraph. If the results from the confirmation test are not conclusive, testing must be repeated with up to 2 (two) additional batches representing the production.

Subsection I

Light Sources

Article 47. The light source should be accompanied by the manufacturer's spectral specification, and be in accordance with the protocol defined by the company.

Article 48. Appropriate temperature control should be kept to minimize its influence on test results, or a control sample may be used in the absence of light, under the same environment conditions.

Article 49. A light source similar to D65/ID65 emission standard may be used as an artificial fluorescent lamp, combining visible and UV emission.

Paragraph 1. The internationally acknowledged standard for daylight, according to definition in ISO 10977(1993), is D65.

Paragraph 2. The equivalent to indoor indirect light standard is ID65.

Paragraph 3. Filter(s) must be used to eliminate radiations, for light sources that emit significant radiation under 320nm.

Article 50. The sample may also be exposed to the combination of cold fluorescent white lamp, similar to ISO 10977(1993) and the UV fluorescent lamp with spectrum distributed between 320nm and 400nm, and maximum energy emission between 350nm and 370nm.

Sole paragraph. A significant proportion of ultraviolet light should be between 320nm and 360nm, and between 360nm and 400nm.

Article 51. Other conditions may be used when carrying out testing, as long as they are justified.

Subsection II

Procedure

Article 52. The samples should be exposed to at least 1.2 million lux hours, integrated to an ultraviolet energy near at least 200 watt hours/m2 for confirmation tests.

Article 53. The samples may be exposed side by side, using the validated actinometric chemical system, ensuring that the exposure was guaranteed; or during an appropriate period of time, when conditions are monitored by calibrated radiometers or luxmeters.

Article 54. If the protected samples are used as controls to assess the alterations caused by the induced temperature in the process, they should be placed together with the samples being tested.

Subsection III

Sample Presentation

Article 55. Care should be taken to ensure the physical characteristics of the samples being tested are preserved, such as cooling and/or placing the samples into sealed recipients, allowing to minimize alterations of physical state, such as sublimation, evaporation, or fusion.

Paragraph 1. The actions on the caption of this article are taken in order to establish a minimum interference with the irradiation of the samples being tested.

Paragraph 2. Possible interactions between samples and the materials used for protection or recipient components should always be considered.

Article 56. Solid samples should be placed in appropriate glass or plastic recipients, and covered, if necessary, with transparent material.

Sole paragraph. The solid samples provided for in the caption of this article should be spread, so they are not thicker than 3 mm.

Article 57. Liquid samples should be exposed in chemically inert and transparent recipients.

Subsection IV

Sample Analysis

Article 58. At the end of the exposure period in the confirmation test, the samples should be examined for any alteration of physical properties, for content and degradation products, through validated stability indicating methods.

Article 59. Sample considerations should guarantee that they are representative and homogeneous.

Sole paragraph. The analysis of the exposed sample should be carried out together with the control samples, if they are used in the test.

Article 60. Forced degradation testing should be designed to provide appropriate information for the development and validation of the test's methods for confirmation tests.

Sole paragraph. The methods provided for in the caption of this article should be able to separate and detect the decomposition products occurring during the confirmation tests.

Article 61. Confirmation tests should identify the necessary precautions during manufacture or formulation of the drug and the need to use light-resistant package.

Section X

Report

Article 62. The stability testing report should present at least the following information or the technical justification of its absence:

I – identification of the active pharmaceutical ingredient through DCB (Denominação Comum Brasileira – Brazilian Common Denomination), INN (International Non-proprietary Name) or CAS (Chemical Abstract Service);

II – batch number(s);

II – batch size(s);

IV – specification of packaging material;

V – batch manufacturing date(s);

VI – initial date of the test (day/month/year);

VII – number of samples tested per batch;

VIII – number of samples analyzed per period;

IX – storage conditions;

X – frequency of tests and specifications;

XI – results from the following tests:

a) aspect;

b) content and the corresponding analytical method;

c) quantification of degradation products and the corresponding analytical method;

d) microbial limits, when applicable;

e) physical characterization;

f) physical stability; and

f) other tests carried out.

XII – conclusion.

Section XI

Assessment of results

Article 63. The objective of the stability testing is to determine a re-test period or shelf life applicable to all active pharmaceutical ingredient batches that will be produced under the same circumstances.

Article 64. The re-test date and the shelf life are based on the assessment of the information from the stability testing, including the results from physical, chemical, biological, and microbiological tests of at least three batches.

Article 65. The degree of result variation among the batches affects the reliability on the results and the guarantee that a future batch will be completely within the specifications by the re-test date or the validity period established.

Article 66. The absence of a statistical method to assess the results should be justified.

Article 67. Any assessment should cover not only the tests carried out, but also the levels of degradation products and other appropriate items.

CHAPTER III

FINAL PROVISIONS

Article 68. The non-observance of the provisions in this Resolution is considered a health infraction, in the terms of Law no. 6,437 dated 20 August 1977, and the offender is liable to the penalties provided for by that law, without prejudice to the applicable civil, administrative, and criminal responsibilities.

Article 69. This Resolution enters into force on the date of its publication.

DIRCEU BRÁS APARECIDO BARBANO

NORMATIVE INSTRUCTION No. 15, OF NOVEMBER 17th, 2009

It provides for the time periods, schedule and priorities for the first implementation stage of the active

pharmaceutical ingredients (API) registration, defined in the Board of Directors Resolution- RDC No. 57, dated November 17, 2009, to which the companies established in the country and performing the activities of manufacture or import of active pharmaceutical ingredients have to adjust themselves.

The Board of Directors of the Brazilian Health Regulatory Agency, pursuant to the powers vested in it under art. 11, item IV, of ANVISA's Regulation approved by Decree no. 3029, dated April 16, 1999, and pursuant to provisions in item II and in §§ 1 and 3 of article 54, and in item II of article 55 of the Internal Regulation approved under the terms of Attachment I to ANVISA's Regulation no. 354, dated August 11, 2006, published again in the Federal Official Gazette dated August 21, 2006, during the meeting held on April 14, 2009,

whereas health is a right of every person and the duty of the State, guaranteeing political, social and economic measures aimed at reducing the risk of disease and of other worsening to the universal and equal access to the actions and services for its promotion, protection and recovery, under the terms of article 196 of the Constitution of the Brazilian Federative Republic, dated October 5, 1988;

whereas the healthcare actions and services have public relevance, under the terms of article 197 of the Constitution and that the Government is responsible for defining, under the terms of the law, its regulation, inspection and control;

whereas the provisions set forth in Law no. 6360, dated September 23, 1976, and in Decree no. 79094, dated January 5, 1977, regarding the health regulatory system to which the medications, active ingredients, pharmaceutical ingredients, similar products and other products are subject;

whereas Law no. 6437, dated August 20, 1977, which provides for the infringements of the federal health laws and sets forth the respective penalties;

whereas Anvisa's institutional purpose of promoting health protection of the population and its duty of coordinating the Brazilian Health Regulatory System, as set forth in art. 6 and in items I, III and XXII of article 7 of Law No. 9782, dated January 26, 1999;

whereas the guidelines, the priorities and the responsibilities set forth in the Brazilian Medications Policy, enacted by Regulation no. 3916/MS/GM, dated October 30, 1998, aimed at guaranteeing conditions for safety and quality of the medications consumed in the country, promote the reasonable use and the population's access to the ones deemed to be essential;

whereas the provisions set forth in Resolution no. 338, dated May 6, 2004, of the Brazilian Health Board, which approves the Brazilian Pharmaceutical Assistance Policy, defining its principles and strategic axes, including qualification of the existing pharmaceutical assistance services and construction of the Health Regulatory Policy that guarantees the population's access to safe, efficient and qualified services and products;

whereas the Active Pharmaceutical Ingredients Program created through Resolution RDC no. 250, dated September 13, 2005;

whereas RDC Resolution no. 30, dated May 15, 2008, which provides for the compulsory registration of active pharmaceutical ingredients with Anvisa;

whereas Regulation no. 978 dated May 16, 2008, which provides for the list of strategic products, with the Brazilian Unified Health System, with the purpose of cooperating with the development of the Health Industrial Hub and creates the Commission for Review and Update of the referred list;

whereas the need to regulate the active pharmaceutical ingredients registration in Brazil, in order to improve quality control of those products in the country and the health requisites to guarantee efficacy and safety of the medications;

whereas the existence of specific standard, Resolution RDC No. 57, dated November 17, 2009, which provides for the registration of active pharmaceutical ingredients among other provisions, RESOLVES:

Art. 1 The schedule and the priorities for the first implementation stage of the active pharmaceutical ingredients registration is hereby approved, under the terms of Anvisa's Board of Directors Resolution no. 57, dated November 17, 2009.

CHAPTER I
THE DEFINITION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS TO BE SUBMITTED IN THE FIRST IMPLEMENTATION STAGE OF THE RESPECTIVE HEALTH REGISTRATION

Art. 2 The following active pharmaceutical ingredients will be subject to the first implementation stage of the health registration with Anvisa, according to the priority criteria and other provisions defined in the Board of Directors Resolution no. 57, dated November 17, 2009:

I. Cyclosporine
II. Clozapine
III. Clindamycin hydrochloride
IV. Cyclophosphamide
V. Ciprofloxacin
VI. Methotrexate
VII. Carbamazepine
VIII. Lithium carbonate
IX. Phenytoin
X. Phenytoin sodium
XI. Lamivudine
XII. Penicillamine
XIII. Thiabendazole
XIV. Efavirenz
XV. Nevirapine
XVI. Rifampicin
XVII. Ritonavir
XVIII. Zidovudin
XIX. Aciclovir
XX. Ampicillin

CHAPTER II
THE TIME PERIODS FOR THE ADEQUACIES RELATED TO THE FIRST IMPLEMENTATION STAGE OF THE ACTIVE PHARMACEUTICAL INGREDIENTS REGISTRATION

Art. 3 For the active pharmaceutical ingredients defined in Art. 2 of the Normative Instruction herein, the following deadlines are established for the respective adequacies related to provisions set forth by RDC No. 57, dated November 17, 2009:

§ 1. As of February 01, 2010 the companies established in the country that perform activities of manufacturing or import of active pharmaceutical ingredients should petition the request for health inspection by Anvisa in order to issue the respective Certificate of Good Manufacturing Practices of Intermediary Products and Active Pharmaceutical Ingredients.

§ 2. As of July 01, 2010 the companies established in the country performing the activities of manufacture or import of the active pharmaceutical ingredients defined in the heading of this Article should petition the respective request for registration with Anvisa.

§ 3. The date of December 30, 2010 is hereby defined as the limit date to petition for the health registration of the active pharmaceutical ingredients referred in the Normative Instruction herein.

Art. 4. This Normative Instruction shall be in full force and effect as of its publication date.

DIRCEU RAPOSO DE MELLO

NORMATIVE INSTRUCTION No. 3, OF JUNE 28th, 2013

It provides for the time periods and the schedule for the second implementation stage of the active pharmaceutical ingredients registration, defined in the Board of Directors Resolution- RDC No. 57, dated November 17, 2009, to which the companies established in the country and performing the activities of manufacture or import of active pharmaceutical ingredients and the medications and intermediary products containing them have to adjust themselves.

The Board of Directors of the Brazilian Health Regulatory Agency, pursuant to the powers vested in it under art. 11, item IV, of ANVISA's Regulation approved by Decree no. 3029, dated April 16, 1999, and pursuant to provisions in item II and in §§ 1 and 3 of article 54, and in item II of article 55 of the Internal Regulation approved under the terms of Attachment I to ANVISA's Regulation no. 354, dated August 11, 2006, published again in the Federal Official Gazette dated August 21, 2006, during the meeting held on June 20, 2013, resolves:

Art. 1 The schedule for the second implementation stage of the active pharmaceutical ingredients registration is hereby approved, under the terms of Anvisa's Board of Directors Resolution no. 57, dated November 17, 2009.

Art. 2 According to the priority criteria and other provisions defined in the Board of Directors Resolution no. 57, dated November 17, 2009, the following active pharmaceutical ingredients will be subject to the second implementation stage of the health registration:

I - The APIs Azithromycin, Benzyl penicillin, Cabergoline, Carboplatin, Cephalexin, Cephalothin, Ceftazidime, Cisplatin, Clarithromycin, Ceftriaxone as well as their respective salts, esters, ethers and hydrates;

II - The salts, esters, ethers and hydrates of the active pharmaceutical ingredients listed in the Normative Instruction no. 15/09.

Art. 3 For purposes of trade and use of the APIs referred to in this Normative Instruction, the following time periods are defined for adequacy:

I – As of January 1st, 2014 the companies established in the country performing the activities of manufacture or import of active pharmaceutical ingredients, medications and intermediary products containing the active pharmaceutical ingredients defined in Items I and II of article 2 should petition the respective registration with ANVISA.

II - As of January 1st, 2015 the companies established in the country performing the activities of manufacture or import of active pharmaceutical ingredients, medications and intermediary products containing the active pharmaceutical ingredients defined in Items I and II of article 2 that have not petitioned or for which the petition for registration has been denied by Anvisa will not be allowed to import and/or trade the API in question.

III - As of January 1st, 2016** the companies established in the country performing the activities of manufacture or import of active pharmaceutical ingredients, medications and intermediary products containing the active pharmaceutical ingredients defined in Items I and II of article 2 that do not have the respective registrations granted by Anvisa will not be allowed to import and/or trade the API in question.

Art. 4. This Normative Instruction shall be in full force and effect as of its publication date.

DIRCEU BRÁS APARECIDO BARBANO

** Modified by NORMATIVE INSTRUCTION No. 6, DATED DECEMBER 18, 2015: “As of January 1st, 2017…”

INFORMATION NOTICE NO. 01 – COIFA/GGMED/SUMED/ANVISA, OF JANUARY 5th, 2015

Subject	**Drug Master File (DMF) restricted part attachment by the API manufacturer**

1 Item 4.10 of Resolution RDC n° 57/2009, which provides on API registration, allows the API manufacturer to send the technical documentation, required for registration purposes, directly to Anvisa. In order to keep the secrecy of some of these information required for registration, many manufacturers choose such alternative.

2 Currently, this technical documentation is submitted in Anvisa, both at the initial application and for amendments of the dossier deficiencies, as letters or attachments, which hinders the documentation sent from being traced.

3 With the intend of improving such procedure, the following code was created:

10731 – INSUMOS FARMACÊUTICOS ATIVOS – Aditamento DMF parte fechada
(10731 – ACTIVE PHARMACEUTICAL INGREDIENTS – attachment of the DMF restricted part)

3.1 With this subject code and the process number, a file number will be created at the moment the documentation is received, to which the API manufacturer may refer.

3.2 Therefore, from now on, we advise manufacturers to follow the instructions below to submit documents to be attached to the API registration application:

I- *The documentation (DMF or amendments of the dossier deficiencies) should be submitted to Anvisa by mail or personally delivered at GEDOC.*

Address: ANVISA
Setor de Indústria e Abastecimento (SIA)
Trecho 5, Área Especial 57,
Brasília-DF - CEP 71205-050

II- *In order to speed up the process, we recommend registration applicants to advise foreign API manufacturers to submit the updated version of the DMF - restricted part as soon as the process number is created. To be attached to the initial submission, the documentation should have its title page completed as the exemplary appended.*

III- *Considering the importance of complete identification of the documents submitted, including file number; considering that this number is created just after the initial application and also considering the time it takes for the documentation sent by mail to arrive in Anvisa, this Agency allows a maximum period of 30 days from the initial application date for the submission of the remnant documentation that is to be attached to the API dossier.*

IV- *The API register application has to include all documents required by the RDC n° 57/2009. Therefore, incomplete applications are susceptible to immediate rejection. We thus recommend strict observance of the deadlines to attach documents to the initial application.*

V- *In order to amend to the letter of deficiencies, the documentation should have its title page completed as the exemplary appended below and include a copy of the letter of deficiencies. The deadline is the same as the one established for the response to the letter of deficiencies.*

VI- *The documentation should be submitted preferably in a digital version of an indexed and searchable pdf file.*

VII- *If the digital file is protected by use of a safety key, this should be informed at petitioning or requirement fulfilling, by the deadline established above.*

VIII- *The safety key may be sent to the institutional e-mail address for API registration, as long as the message is duly identified with the information on the title page as the model attached.*

E-mail for the API Registration Coordination:
coifa@anvisa.gov.br

Annex: Title Page – Application Form *

*Foreign companies don´t need to fill out information related to CNPj and legal representatives

PETIÇÃO

Application

(Somente para peticionamento manual)

Nome da Empresa:
Nome da empresa solicitante do registro do insumo farmacêutico ativo
Company´s name (Brazilian Applicant)

CNPJ:
(Deixar em branco)
Corporate Taxpayer ID (Foreign Companies may leave it blank)

Identifique a Modalidade de Petição:

☐ **Petição Primária** ☒ **Petição Secundária**

Nº do Processo: (Somente para petição secundária)
Nº do processo a que se refere
Process number

Código e Assunto de Petição: (utilizar código e assunto existentes na tabela do peticionamento eletrônico no sítio eletrônico da ANVISA, quando couber)

DMF restricted part attachment by the API manufacturer

10731 - Aditamento DMF parte fechada

Nº de folhas apresentadas neste ato: (Excluída esta folha de rosto)
Number of paper sheets

Nº do Expediente : (Preenchimento Exclusivo da Anvisa)
File number (filled out by Anvisa)

Gerência-Geral, Gerência ou Unidade a que se destina:
COIFA-GGMED

Observações:
Remarks

Place and Date | Legal representative´s name | Legal representative´s signature

Local e data	Nome do Responsável Legal ou Representante Legal	Assinatura do Responsável Legal ou Representante Legal