Registration of Active Pharmaceutical Ingredients

ANVISA Normative Instruction n. 15 and Resolution – RDC n. 57, of November 17th, 2009

NORMATIVE INSTRUCTION N.15, OF NOVEMBER 17TH, 2009

The Collegiate Board of Directors of the Brazilian Sanitary Surveillance Agency, in the use of the attribution vested in it by the Article 11, clause IV, of the Regulation of ANVISA approved by Decree n. 3.029, of April 16, 1999, and in view of what is determined by the proposition II and paragraphs 1st and 3rd of the article 54, and the proposition II of the Article 55 of the Internal Regulation approved by the terms of the Annex I of the ANVISA's Bylaw n. 354, of August 11th, 2006, republished in the Federal Official Journal of August 21, 2006, in meeting held on April 14th, 2009,

• whereas that the health is the people's right and a government commitment, ensuring througout of social and economic policies, the reduction of the illness' risk and other related problems and also the equal and universal access to health actions and services for its promotion, protection and recovery, on the terms of the article 196 of the Federative Republic of Brazil Constitution, of October 5th, 1988;

• whereas that the health actions and services are of the public relevance, in the terms of the article 197 of the Constitution, being the Public Power responsible to make use, in the terms of the law, on its regulamentation, fiscalization and control;

• whereas the dispositions contained in the Law n. 6,360, of September 23rd, 1976, and its Decree n. 79,094, of January 5th,1977, concerning to the sanitary surveilance system which regulates drug products, pharmaceutical ingredients, medical devices and other products;

• whereas the Law n. 6.437, of August 20th, 1977, which defines the violations to the federal sanitary legislation and establishes the respective penalties;

• whereas the Anvisa's institucional purpose to promote the protection of the health for the population and its duty to co-ordinate the National Sanitary Surveilance System, established by the Law n. 9,782 of January 26th, 1999, article n.6 and items I, III and XXII of article n.7;

• whereas the lines of direction, priorities and responsibilities established by the National Drug Policies, enforced by the Bylaw n. 3.916/MS/GM, of October 30th, 1998, that ensures the conditions of safety and quality for the medicines used in the country, promoting the rational use and facilitating the access of the population to those drugs considered essential;

• whereas the dispositions included in the Resolution n. 338, of May 6th, 2004, of the National Council of Health, that approved the National Policies of the Pharmaceutical Assistance, defining the principles and strategies, including the existing pharmaceutical assistance services qualification and the construction of a Sanitary Surveilance Policy that enables the access of the population to services and products, safe, efficient and with quality;

• whereas the Active Pharmaceutical Ingredients Program established by the Resolution – RDC n. 250, of September 13th, 2005;

• whereas the Resolution – RDC n. 30, of May 15th, 2008, that establishes the obligation to register active pharmaceutical ingredients on the Anvisa's cadastre;

• whereas the Bylaw n. 978, of May 16th, 2008, that established the list of strategical products, in the scope of the Unique System of Health, with the purpose of – collaborating with the development of Health Industrial Complex and – the creation of a Commission for Revision and Update of this related list;

• whereas the need to regulate the registration of active pharmaceutical ingredients in Brazil, to improve the quality control of these products in the country and the sanitary requirements to ensure efficacy and safety of the medicines, considering the existence of a specific regulation Resolution RDC n. 57, of November 17th, 2009, that enforces the registration of active pharmaceutical ingredients (IFA – initials in portuguese) and provide other steps,

DECIDE:

Article 1. *It is approved the schedule and priorities for the first stage of the implementation of the active pharmaceutical ingredients (IFA – initials in portuguese), in the terms of the Resolution n. 57, of November 17th, 2009 of the Anvisa Collegiate Board of Directors.*

CHAPTER I – DEFINITION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS (IFA) TO BE SUBMITTED IN THE FIRST STAGE OF THE IMPLEMENTATION OF THE SANITARY REGISTRATION

Article 2. *The following active pharmaceutical ingredients (IFA) will be subject to the first stage of the implementation of the sanitary registration in Anvisa, according to the criteria of priority and other dispositions defined in the Resolution of Collegiate Board of Directors n. 57, of November 17th, 2009:*

I. *Cyclosporin*
II. *Clozapine*
III. *Clindamycin Hydrochloride*
IV. *Cyclophosphamide*
V. *Ciprofloxacin*
VI. *Methotrexate*
VII. *Carbamazepine*
VIII. *Lithium Carbonate*
IX. *Phenytoin*
X. *Phenytoin Sodium*
XI. *Lamivudine*
XII. *Penicilamine*
XIII. *Thiabendazole*
XIV. *Efavirenz*
XV. *Nevirapine*
XVI. *Rifampicin*
XVII. *Ritonavir*
XVIII. *Zidovudine*
XIX. *Acyclovir*
XX. *Ampicillin*

CHAPTER II – TIMELINES FOR COMPLIANCE TO THE FIRST STAGE OF THE IMPLEMENTATION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS (IFA) REGISTRATION

Article 3. *For the active pharmaceutical ingredients (IFA) defined in the Article 2 of the present Normative Instruction, is established that the following periods for the respective adequacy to what is referred in the RDC n. 57 of November 17th, 2009:*

Paragraph 1. *Starting on February 1st, 2010, the companies established in the country which exercise the activities of active pharmaceutical ingredients manufacturing or import will have to submit the request for sanitary inspection to Anvisa for the issuance of the Good Manufacturing Practices of Intermediate Products and Active Pharmaceutical Ingredients Certificate.*

Paragraph 2. *Starting on July 1st, 2010, the companies established in the country which exercise the activities of active pharmaceutical ingredients manufacturing or import included in the scope of this Article, will have to submit the respective request for such ingredients registration to Anvisa.*

Paragraph 3. *It is established that December 30th, 2010 is the last date for the active pharmaceutical ingredients referred by this Normative Instruction, to have its sanitary registration submitted to ANVISA.*

Article 4. *This Resolution enters into force on the date of its publication.*

DIRCEU RAPOSO DE MELLO

ANVISA RESOLUTION – RDC N. 57, OF NOVEMBER 17TH, 2008

The Collegiate Board of Directors of the Brazilian Sanitary Surveillance Agency, in the use of the attribution vested in it by article 11, clause IV, of the Regulation of ANVISA approved by Decree n. 3.029, of April 16, 1999, and in view of what is determined by the proposition II and paragraphs 1st and 3rd of the article 54, of the Internal Regulation approved by the terms of the Annex I of the ANVISA's Bylaw n. 354, of August 11th, 2006, republished in the Federal Official Journal of August 21, 2006, in meeting held on April 14th, 2009,

• whereas that the health is the people's right and a government commitment, ensuring throughout of social and economic policies, the reduction of the illness' risk and other related problems and also the equal and universal access to health actions and services for its promotion, protection and recovery, on the terms of the article 196 of the Federative Republic of Brazil Constitution, of October 5th, 1988;

• whereas that the health actions and services are of the public relevance, in the terms of the article 197 of the Constitution, being the Public Power responsible to make use, in the terms of the law, on its regulamentation, fiscalization and control;

• whereas the dispositions contained in the Law n. 6,360, of September 23rd, 1976, and its Decree n. 79,094, of January 5th,1977, concerning to the sanitary surveilance system which regulates drug products, pharmaceutical ingredients, medical devices and other products;

• whereas the Law n. 6.437, of August 20th, 1977, which defines the violations to the federal sanitary legislation and establishes the respective penalties;

• whereas that the health is a fundamental right for the human being and having the State the responsibility to provide the indispensable condition to its full exercise, as foreseen in the article n. 2 of the Health Organic Law (LOS – initials in portuguese), Law n. 8,080, of September 19th, 1990;

• whereas the Anvisa's institucional purpose to promote the protection of the health for the population and its duty to co-ordinate the National Sanitary Surveilance System, established by the Law n. 9,782 of January 26th, 1999, article n. 6 and items I, III and XXII of article n. 7;

• whereas the lines of direction, priorities and responsibilities established by the National Drug Policies, enforced by the Bylaw n. 3.916/MS/GM, of October 30th, 1998, that ensures the conditions of safety and quality for the medicines used in the country, promoting the rational use and facilitating the access of the population to those drugs considered essential;

• whereas the Resolution n. 338, of May 6th, 2004, of the National Council of Health dispositions, that approved the National Policies of the Pharmaceutical Assistance, defining the principles and strategies, including the existing pharmaceutical assistance ser-

vices qualification and the construction of a Sanitary Surveilance Policy that enables the access of the population to services and products, safe, efficient and with quality;

• *whereas the Resolution – RDC n. 249, of September 13th, 2005, that establishes the Good Manufacturing Practices for Intermediate Products and Pharmaceutical Ingredients;*

• *whereas the Active Pharmaceutical Ingredients Program established by the Resolution – RDC n. 250, of September 13th, 2005;*

• *whereas the Resolution – RDC n. 30, of May 15th, 2008, that establishes the obligation to register active pharmaceutical ingredients on the Anvisa's cadastre;*

• *whereas the Bylaw n. 978, of May 16th, 2008, that established the list of strategical products, in the scope of the Unique System of Health, with the purpose of – collaborating with the development of Health Industrial Complex and – the creation of a Commission for Revision and Update of this related list;*

• *whereas the need to regulate the registration of active pharmaceutical ingredients in Brazil, to improve the quality control of these products in the country and the sanitary requirements to ensure efficacy and safety of the medicines,*

adopts the following Resolution of the Collegiate Board of Directors and I, the Chairman, determine its publication:

Article 1. *Aprove the Technical Regulation for Active Pharmaceutical Ingredients (API) Registration in Brazil, in the terms of the ANNEX of this Resolution.*

Article 2. *The Active Pharmaceutical Ingredients, including the imported ones, after the period of adequacy that article 3 of this resolution, cannot be industrialized, displayed for sale or commercialized in the country, before being registered by Anvisa, with the exception of active pharmaceutical ingredient which would be used for scientific or technological research, as well as for the research and development of formulations.*

Paragraph 1. *The registration of active pharmaceutical ingredients destined exclusively for export will be optional.*

Paragraph 2. *The registration that the caption of this article is related will be valid for 5 (five) years and can be renewed by equal and successive periods as long as the number of the initial registration is kept.*

Paragraph 3. *The registration renewal must be submitted on the first semester of the last (5th) year of validity, counted from the date of publication of such registration, considering itself automatically renewed, independently of decision, if such renewal has not been pronounced until the date of the first registration expiration.*

Paragraph 4. *The register of the product whose revalidation has not been requested in the stated period defined in Paragraph 2 of this article, will be declared extinct.*

Paragraph 5. *The register of the active pharmaceutical ingredients that this resolution deals with, will not be granted when conditions, requirements and procedures foreseen in this regulation are not complied.*

Paragraph 6. *Anvisa is entitled, in emergencial or temporary situation, to exempt from registration active pharmaceutical ingredients destinated to the exclusive use in the production of drug products to be used in public health programs for the Ministry of Health and its entailed entities.*

I – *The dismissal of active pharmaceutical ingredients registration referred in paragraph 5th, will be under exclusive approval of the ANVISA's Collegiate Board of Directors, by a formal and public act signed by its President.*

Article 3. *The companies established in the country which exercise the activities of manufacturing or import active pharmaceutical ingredients, must adjust its activities to what is defined in this Resolution, according to a schedule approved by the Collegiate Board of Directors, that also contains the list of substances in order and classification according to the following criteria of adequacy priority:*

I – *Drug substances with low Therapeutical Index.*

II – *Drug substances produced in the country.*

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

IV – *Drug substances used for the production of medicines included in the Ministry of Health Strategical Programs.*

V – *Drug substances used for the production of medicines included in the National List of Essential Medicines (Rename – initials in portuguese).*

VI – *Drug substances used for the production of medicines dispensed in exceptional situations.*

VII – *Drug substances used for the public production of medicines for neglected illnesses, according to the Ministry of Health definition.*

VIII – *Drug substances used for the production of medicines that belongs to the therapeutical categories of antineoplasics, antibiotics and immunosuppressants.*

IX – *Drug substances used for the production of generics.*

X – *Drug substances used for the production of medicines destinated to the basic health attention.*

Only Paragraph. *The publication of the referred schedule in this article will be made by a proper normative act from ANVISA's Collegiate Board of Directors and it will establish the period for companies adequacy.*

Article 4. *The active pharmaceutical ingredients present in the composition of imported medicines, either under half-elaborated form or finished product, must be registered according to the scope of this resolution.*

Article 5. *The disobedience to what is described in the present Resolution and in its approved Regulation, constitutes a sanitary infraction in the terms of the Law n. 6437, of August 20th, 1977, subjecting to civil, administrative and criminal liabilities.*

Article 6. *This Resolution enters into force on the date of its publication.*

DIRCEU RAPOSO DE MELLO

ANNEX – TECHNICAL REGULATIONS FOR THE REGISTRATION OF ACTIVE PHARMACEUTICAL INGREDIENTS (IFA)

1. PURPOSE

To set forth the requirements for registration of active pharmaceutical ingredients with the purpose of ensuring the quality and allowing their use in the elaboration of pharmaceutical products in the country.

2. COMPREHENSIVENESS

These regulations apply to the companies established in the country exercising activities of manufacturing or importing active pharmaceutical ingredients and refer to all active pharmaceutical ingredients, national or imported.
2.1 *The resolution applies to synthetic pharmaceutical ingredients used in the manufacture of medicines.*
I- *The registration of the API used in phytotherapic medicines, dynamized and biological products, including serums and vaccines shall be discussed in separate specific regulations.*

3. DEFINITIONS

For effect of these Technical Regulations, the following definitions are adopted:
3.1 *Common Brazilian Name (DCB – initials in portuguese) – Name of the medicine or pharmacologically active ingredient approved by the Federal Agency responsible for Sanitary Surveillance.*
3.2 *Common International Name (DCI – initials in portuguese) – Name of the medicine or pharmacologically active ingredient recommended by the World Health Organization.*
3.3 *Specification – Is the detailed description of the requisites the products or materials used or obtained during the manufacturing shall fulfill. Serves as basis for quality assessment.*
3.4 *Manufacture – All operations including the purchase of materials, production, quality control, release, storage, finished products issuance and related controls.*
3.5 *Impurity – Any undesired compound present in the intermediate or in the active pharmaceutical ingredient.*
3.6 *Active Pharmaceutical Ingredient (API) – Also called drug or simply active ingredient, is the pharmacologically active compound destined to be used in medicine.*
3.7 *Batch – Specific quantity of product obtained by a process or a series of process, in a manner that it is homogeneous, within the limits set forth. In case of continuous production, a batch can correspond to a defined fraction of the production, determined by a pre-fixed amount of mass or by the produced amount in a fixed time interval.*
3.8 *Raw-material – Active or inactive substances used for the manufacture of ingredients, even though they remain unchanged, experience modifications or are eliminated during the manufacturing process.*
3.9 *Material – Term used generically, including raw-material, auxiliary and intermediate materials, active pharmaceutical ingredients, packaging and labeling materials.*
3.10 *Packaging material – Any form of packaging destined to protect and maintain the intermediates and active pharmaceutical ingredients, including labeling material.*
3.11 *Starting Material – Material of chemical and/or biological origin which shall originate an intermediate product or pharmaceutical ingredient.*
3.12 *Starting Material – Chemical used in the production of an active pharmaceutical ingredient, incorporated thereto as an important structural element. The starting material has the denomination, chemical structure, properties and physical chemical characteristics and impurities profile well defined.*
3.13 *Batch Number – Any combination of numbers or letters through which one can track the complete history of the manufacture of the batch and its operation in the market.*
3.14 *Primary reference standard – Substance which high degree of purity and authenticity have been demonstrated by analytic tests.*
3.15 *Secondary reference standard – Substance of established quality and purity, after comparison with a primary reference standard.*
3.16 *Polymorphism – Is the property of certain substances of presenting more than one crystalline form.*
3.17 *Validity Term – Time during which the product can be used, characterized as useful life period and grounded on the specific stability studies.*
3.19 *Process – Set of unit operations, compliant with techniques, standards and specifications.*
3.20 *Production of Active Pharmaceutical Ingredient – Set of operations involved in the preparation of an intermediate product or active pharmaceutical ingredient, since the receipt of the materials of the storage room, through processing and packaging.*
3.21 *Finished product – Product which has gone through all stages of production, packaging and labeling.*
3.22 *Chiral – Molecules of identical chemical composition, but which mirrored images cannot be superimposed.*
3.23 *Label – Identification printed, lithographed, painted, fireengraved, pressure or self-adhesive, applied directly on vials, packages, enclosures or any inner or outer package protector, and cannot be removed or changed during the use of the product and 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 attesting that any*

procedure, process, equipment, material, operation or system really should lead to the expected results.
3.26 *CAS Number – The number of registration with the Chemical Abstract Service (CAS). It is a numerical identifier containing a maximum of 9 digits, divided in 3 parts. Each CAS registration number is unique, assigns only one substance, it has no chemical meaning and is one link to a rich source of information on a specific chemical substance.*
3.27 *Intermediate – Product partially processed that should go through more manufacturing stages prior to the obtention of the active pharmaceutical ingredient.*
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 – A measure of the excess, normally expressed in percentage terms, of the enantiomer of interest on the total mixture of enantiomers.*
3.30 *Technical Report – Conclusive document presented by the company, containing the information characterizing the product and fulfilling the demands of the sanitary authority which may issue a decision on the registration.*

4. REGISTRATION DOCUMENTATION

In the act of filing the active pharmaceutical ingredient, the company shall file one unique process, instructed with the following documentation:
4.1. *Petition forms duly completed.*
4.2. *Original copy of the proof of collection of the sanitary surveillance inspection fee or proof of exemption, when applicable.*
4.3. *Copy of the Working Permit of the company up to date (Health Permit).*
4.4. *Copy of the Working Permit of the company and Special Working Permit, when applicable, published in the Union's Official Gazette.*
4.5. *Copy of the Certificate of Good Manufacturing Practices and Control of Pharmaceutical ingredients, up-to-date, issued by Anvisa or proof of the Technical-Operational Conditions issued by the local sanitary authority or a protocol requesting the inspection of the local sanitary authority, provided that it presents a satisfactory status according to the last inspection.*
4.6. *For imported API, present a copy of the Certificate of Good Manufacturing Practices and Control of Pharmaceutical ingredients, up-to-date, issued by Anvisa or a protocol requesting the inspection of Anvisa, provided that it presents a satisfactory status according to the last inspection.*
4.7. *Copy of the Technical Responsibility Certificate in effect, of the company requesting the registration, issued by the Regional Chemistry or Pharmacy Council.*
4.8. *Proof of cadastre made of the API in ANVISA.*
4.9 *Documents required in the laws in effect on the control of Transmissible Spongiform Encephalopathies (TSEs).*
4.10 *Technical report containing the information described in item 5, below. All documents of item 5 shall be presented in a paper with the letterhead of the company manufacturing the active pharmaceutical ingredient in Portuguese Language (see Resolution approved by DICOL). It is an option of the manufacturer(s) of the drug(s) to submit, directly to ANVISA, the documents explicated herein, duly identified with the process number they are related to.*

5. TECHNICAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT

The documents for registration shall also contain the following information:
5.1. *General information:*
a) *Nomenclature: Common Brazilian Nomenclature, or, in the lack thereof, Common International Nomenclature.*
b) *CAS No.*
c) *Chemical name.*
d) *Synonyms with complete reference.*
e) *Molecular and structural formula.*
f) *Molecular weight.*
g) *Physical form.*
h) *Melting or boiling point.*
i) *Solubility.*
j) *Loss on drying.*
k) *Physical characteristics (crystalline, amorphous, particle size, solvatation, etc.).*
l) *pka and pH.*
m) *Storage conditions.*
n) *Organoleptic properties.*
5.2. *API manufacturing process:*
a) *Manufacturer(s): Name, full address, company responsible for each step of the manufacture process and quality control (including contractors, third parties).*
b) *Description of the productive process, including materials, equipment and operation conditions (for instance, temperature, pressure, pH, time, speed, agitation ranges, etc.); and the controls in process.*
c) *Identification in the critical stages including the respective acceptance tests and criteria.*
d) *Flowchart of the productive process with indication of the formation of intermediates and possible impurities, including the elucidation of the respective chemical structures.*
e) *Indication of the raw-materials, solvents, catalyzers, etc...*
f) *Indicate the production scale and yield.*
g) *Specifications of raw-materials and packaging materials.*
5.2.1 *Characterization:*
Physical-chemical trials allowing the due characterization of the API structure:
a) *Analyses of one industrial batch proving the functional groups, the chemical structure and molecular form expected for the API.*
b) *Possible Isomers.*

c) *Polymorphism, discriminating 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 of the synthesis, with brief description and indication of origin.*
b) *Organic Impurities (of the process and related substances): Raw-materials (starting), related products, intermediate products, degradation products, reagents and catalyzers.*
c) *Inorganic Impurities: Reagents and catalyzers, heavy metals, inorganic salts.*
d) *Residual solvents.*
5.3. *Quality control of the API:*
5.3.1 *Specifications*
b) *Aspect.*
c) *Identification.*
d) *Assay.*
e) *Impurities (organic, inorganic and residual solvents).*
f) *Physical-chemical properties (pH, melting point, etc).*
g) *Granulometric distribution.*
h) *Polymorphism, including the analytic methodology adopted and results of the tests for determination of the probable polymorphs of the ingredient.*
i) *In the ingredients presenting chirality, data on the content of the stereoisomers.*
j) *Moisture.*
k) *Microbiologic limits: Sterility, endotoxins (if applicable).*
l) *Specific optic rotation (if applicable).*
5.3.2 *Copy of a quality control report of three batches produced, with API identification, batch number, reference values and results of the tests carried out.*
5.3.3 *Description of the analytic methodology:*
Validation of analytic methodology according to the specific technical regulations in effect for the validation of analytic and bioanalytic methods, when a pharmacopeic methodology is not used.
In case of pharmacopeic methodology, the company shall present the covalidation of the method.
5.4 *Packaging Material: Description and specification of the material in the primary packaging.*
5.5 *Stability and Photo-stability Report:*
The stability and photo-stability studies shall be conducted according to the specific technical regulations in effect in Brazil.

6. REGISTRATION RENEWAL DOCUMENTATION

For the renewal of the registration of active pharmaceutical ingredients, the company shall present the following documents:
6.1. *Petition forms duly completed.*
6.2. *Original copy of the proof of collection of the sanitary surveillance inspection fee or proof of exemption, when applicable.*
6.3. *Copy of the Certificate of Good Manufacturing Practices and Control (CBPFC) issued by ANVISA for the active pharmaceutical ingredient, object of registration renewal, or copy of the protocol of request of inspection for purposes of issuance of the CBPFC, provided that it was satisfactory in the last inspection.*
6.4. *In case of ingredients registered exclusively for purposes of exporting, according to these regulations, a proof of export shall be presented.*
6.5. *List of all changes and/or inclusions post-registration occurred during the last validity term of the registration of the product.*
6.6. *Conclusive results of long-duration stability studies, according to a specific guide defined by Anvisa.*