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 its 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).


4.5. 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.