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ANVISA publishes resolutions on new procedures relative to marketing authorization in Brazil: RDC #58 and #60/2014

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The main law regulating the health system in Brazil – Law #6,360 dated 1976 – establishes that each and every drug available in the pharmaceutical market must be approved by the Ministry of Health. Since the creation of the Brazilian FDA (called ANVISA), this autonomous autarchy subordinated to the Ministry of Health is in charge of issuing marketing authorization for drugs for human use and of establishing specific resolutions in order to regulate each of the existing categories of medicaments, such as the new drugs, generics, similars, biologicals.

According to ANVISA's requirements, the documentation submitted by the manufacturers of both generic and similar drugs, upon applying for marketing approval, is significantly simplified compared to the reference product (the so-called “abridged process”), as only pharmaceutical equivalence and relative bioavailability/ bioequivalence assays are required to obtain approval for products pertaining to these categories.

It should be noted that, since the publication of Resolutions RDC #133 (new applications for marketing approval) and RDC #134 (similars, already approved), both dated May 29, 2003, ANVISA has begun to require proof of therapeutic equivalence also for similar drugs; therefore, it is estimated that all manufacturers of these products will have complied with such requirement by the end of 2014.

Accordingly, studies of pharmaceutical equivalence and bioavailability/bioequivalence became necessary in order to obtain marketing authorization for both generic and similar drugs, although the latter were not then yet considered to be interchangeable with the reference product.

In this sense, Resolution **RDC #58**, published on October 10, 2014, now provides legal basis establishing interchangeability of similar drugs with their corresponding reference drugs.

This measure, that is to be adopted by all manufacturers by January 1, 2015, permits applicants who are seeking approval for similar drugs, once having evidenced their pharmaceutical equivalence with respect to the reference products, to declare in the package leaflets that they are equivalent substitutes for the reference drugs.

Applicants will then have a period of 1 year, counted from the date of their inclusion in the list of interchangeable products approved by ANVISA, to amend the package leaflets, which will contain the text “SIMILAR DRUG EQUIVALENT TO THE REFERENCE DRUG”.

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Furthermore, on October 10, 2014, ANVISA also published Resolution **RDC #60/2014**, establishing revised criteria for the granting and renewal of marketing approval for three distinct categories of drugs. This regulation seeks to update and harmonize technical requirements of quality, safety and efficacy for the registration of drugs classified as new, generic and similar.

Prior to its publication, RDC #60/2014 was brought for discussion in a public consultation during a 90-day period, having been object of comments and suggestions mainly from health professionals, representatives of the regulated sector and members of ANVISA's several divisions.

The new regulation consolidates the criteria and minimum documentation required for the marketing approval of these categories of medicaments into a single resolution, replacing Resolutions RDC #136/2003, #16/2007 and #17/2007, previously in force.

Resolution RDC #60/2014 also comes to implement the electronic filing of applications for marketing approval before ANVISA, and to update and restructure the technical report to be presented according to the Common Technical Document (CTD) from the International Conference on Harmonization of Technical Requirements for Marketing Approval for Pharmaceuticals for Human Use (ICH).

As this is a very recent resolution, it is not clear how ANVISA will analyze the whole process from now on. Resolution RDC #60/2014 shall come into force 90 days after its publication in the Federal Official Gazette. Attached to this newsletter, you will find copies of ANVISA's RDCs #58 and #60/2014.

Should you have any queries and/or wish to receive more details hereon, please do not hesitate to contact us. We will be glad to assist you in this respect.

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RESOLUTION – RDC N° 58, OF OCTOBER 10th, 2014

This Resolution establishes measures to be adopted at ANVISA by the holders of drug registrations for interchangeability between similar drugs and reference drug.

The Board of Directors of the National Sanitary Surveillance Agency (ANVISA), in exercise of the powers conferred by items III and IV, of Article 15 of Law No. 9,782, dated January 26, 1999, item V, and §§ 1st and 3rd of Article 5 of the Bylaw approved in terms of Annex I of ANVISA's Ordinance No. 650, of May 29, 2014, in view of items III, of Article 2nd, III and IV, of Article 7th of Law No. 9,782 of 1999, the Agency Regulatory Process Improvement Program, established by Ordinance No. 422, of April 16, 2008, at a meeting held on October 9, 2014, adopts the following Board Resolution and I, the Director-President, determine its publication:

Article 1 – This Resolution determines the measures to be adopted at ANVISA by the holders of drug registrations for interchangeability between similar drugs with their respective reference drugs.

§ 1 – The adoption of the measurements established in this Resolution is mandatory for all holders of drug registrations of which studies mentioned in Article 2nd have been approved by ANVISA.

§ 2 – Prescription-free drugs are not covered by this Resolution.

Article 2 – Will be considered interchangeable the similar drug of which pharmaceutical equivalence, relative bioavailability/bioequivalence or bioisention studies have been submitted, analyzed and approved by ANVISA.

Sole paragraph – ANVISA will publish in its website a list of similar drugs indicating the reference drugs with which they are interchangeable.

Article 3 – The information regarding the interchangeability referred to in Article 2 will be included in the package leaflet of the similar drug.

Article 4 – The notification for changing the package leaflet text must be electronically filed, according to the subject-specific code, and must follow the guide for electronic submission of package leaflet text.

§ 1 – The companies holding interchangeable similar drug registrations will have a term of 1 (one) year counted as from the date of its inclusion in the list referred to in Article 2 to notify ANVISA about the package leaflet adaptation, under the *caput* of this article.

§ 2 – The adaptation referred to in the previous article requires immediate implementation and is independent on ANVISA's manifestation.

§ 3 – Interchangeable similar drugs of which package leaflet are not changed within the term defined in § 1 of this article will not be accepted for sale in the country.

§ 4 – The drugs produced until the notification for changing the package leaflet may be marketed until the end of its validity.

Article 5 – For evaluation purposes, petitions for similar drug registration renewal of which pharmaceutical equivalence, relative bioavailability/bioequivalence or bioisention studies have not yet been analyzed, ANVISA will publish Normative Instruction defining the criteria and order of evaluation.

Article 6 – The following text is added to Annex 1 of RDC No. 47/2009:

I – DRUG IDENTIFICATION:

...

“For drugs included in the list referred to in Article 2 of RDC No. 58, dated October 10, 2014, include the phrase:

SIMILAR DRUG EQUIVALENT TO THE REFERENCE DRUG”

Article 7 – This resolution comes into force on January 1st, 2015.

DIRCEU BRÁS APARECIDO BARBANO

Director-President

RESOLUTION - RDC No. 60, OF OCTOBER 10th, 2014

This resolution establishes the criteria for the grant and renewal of registration of drugs with synthetic and semisynthetic active ingredients classified as new, generic and similar, and provides other measures.

The Board of Directors of the National Sanitary Surveillance Agency (ANVISA), in exercise of the powers conferred by items III and IV, of Article 15 of Law No. 9,782, dated January 26, 1999, item V, and §§ 1st and 3rd of Article 5 of the Bylaw approved in terms of Annex I of ANVISA's Ordinance No. 650, of May 29, 2014, in view of items III, of Article 2, III and IV, of Article 7 of Law No. 9,782 of 1999, the Agency Regulatory Process Improvement Program, established by Ordinance No. 422, of April 16, 2008, at a meeting held on October 9, 2014, adopts the following Board Resolution and I, the Director-President, determine its publication:

Article 1 – It is approved the Technical Regulation establishing the minimum requirements for the grant and renewal of registration of drugs with synthetic and semisynthetic active ingredients classified as new, generic and similar, pursuant to this Resolution.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 2 – This resolution has the objective of establishing the criteria and the minimum documentation required for the grant and renewal of registration of drugs with synthetic and semisynthetic active ingredients classified as new, generic and similar, in order to ensure quality, safety and efficacy of these drugs.

Section II

COVERAGE

Article 3 – This Regulation applies to all drugs with synthetic and semisynthetic active ingredients classified as new, generic and similar, except those regulated by specific legislation in force.

Section III

Definitions

Article 4 – For purposes of this Resolution the following definitions are adopted:

I - accessory - supplement intended to dose, conduct or perform the administration of the pharmaceutical form to the patient, marketed within the secondary packaging together with the drug, and without direct contact with the pharmaceutical form (Resolution RDC No. 31, dated August 11, 2010);

II - bioavailability - indicates the absorption rate and extent of an active ingredient from a pharmaceutical form, from its concentration/time curve in the systemic circulation or its excretion in the urine, measured by the exposure peak and exposure magnitude or partial exposure;

III - relative bioavailability – comparison of the bioavailability of two products under the same experimental design;

IV - bioequivalence - is the demonstration of equivalent bioavailabilities between products when studied under the same experimental design;

V - biobatch - batch used for proof of pharmaceutical equivalence and bioequivalence;

VI - Good Manufacturing Practices Certificate (GMPC) - document issued by ANVISA attesting that a particular establishment complies with Good Manufacturing Practices established in the sanitary legislation in force;

VII - ATC (Anatomical Therapeutic Chemical) Code - abbreviation used for Anatomical Therapeutic Chemical classification of drugs into different groups and sub-groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties (WHO, 2013);

VIII - quality control - set of measures to ensure, at any time, the production of drug batches that meet the standards of activity, purity, efficacy and safety;

IX - Brazilian Common Denomination (BCD) - generic nomenclature assigned to pharmaceutical ingredients, according to the relation established by the Brazilian Pharmacopoeia;

X - packaging - wrapping, container or any form of packaging, removable or not, to cover, packaging, bottling, protect or maintain, specifically or not, drugs (Law No. 6,360, of September 23, 1976, and Resolution - RDC No. 71, of December 22, 2009);

XI - primary packaging - packaging that is in direct contact with the drug (Resolution - RDC No. 71, of December 22, 2009);

XII - secondary packaging - outer packaging of the product, which is in contact with the primary packaging or intermediate wrap, and may contain one or more primary packaging (Resolution - RDC No. 71, of December 22, 2009);

XIII - functional secondary packaging - one that offers additional protection or serves to release the product dose;

XIV - intermediate wrap - optional packaging that is in contact with the primary packaging and constitutes a wrap or any other form of removable protection, and may contain one or more primary packaging, as approved by ANVISA (Resolution - RDC No. 71, of December 22, 2009);

XV - Pharmaceutical Equivalence Study - set of physicochemical and, where applicable, microbiological and biological tests, proving that two drugs are pharmaceutical equivalents (Resolution - RDC No. 31, of August 11, 2010);

XVI - pharmaceutical equivalents - drugs having the same pharmaceutical form, same route of administration and same amount of the same active substance, i.e. same salt or ester of the therapeutic molecule; they may or may not contain identical excipients, provided that well designed for the intended function; They must comply with the same requirements of individual monograph of the Brazilian Pharmacopoeia, preferably, or with other specific official compendia, standards or regulations approved/endorsed by ANVISA or, in their absence, with other standards of quality and performance. Modified release pharmaceutical forms that require reservoir or excess may or may not contain the same amount of the active substance, provided that they release identical amounts of the same active substance in the same dose range (Resolution - RDC No. 31, of August 11, 2010);

XVII - proportional formulations - drug formulations in which all components of the formulation are exactly in the same proportion in all different dosages or the ratio between the excipients and the total weight of the formulation is within the limits for moderate change of excipients, established in specific legislation in force to post-registration of drugs;

XVIII - radical innovation – development of new molecule not registered in the country;

XIX - incremental innovation - development of improvements in relation to an already registered drug;

XX - active pharmaceutical ingredient (API) - any substance introduced in the formulation of a pharmaceutical form which, when administered to a patient, acts as the active ingredient. Such substances may exert pharmacological activity or other direct

effect in the diagnosis, cure, prevention or treatment of a disease, and may also affect the structure and function of the human body; (Resolution - RDC No. 17, of April 16, 2010 and Resolution RDC No. 45, of August 9th, 2012);

XXI - batch - definite amount of raw material, packaging material or processed product in one or more processes, of which essential feature is the homogeneity. Sometimes it may be necessary to divide a batch into sub-batches, which will then be grouped to form a homogeneous final batch. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by homogeneity (Resolution - RDC No. 17, of April 16, 2010);

XXII - pilot batch - batch of pharmaceutical product produced by a batch that is representative and reproductive of a industrial scale produced batch (Normative Instruction No. 02, of March 30, 2009);

XXIII - raw materials - active or inactive substances used in the manufacture of drugs, both which remain unchanged as those likely to undergo changes (Law 6,360, of September 23, 1976);

XXIV - drug - pharmaceutical, technically obtained or prepared product, with prophylactic, curative, palliative or diagnostic purposes (Law No. 5,991, of December 17, 1973);

XXV - reference drug - innovative product registered in the federal agency responsible for sanitary surveillance and marketed in the country, of which efficacy, safety and quality have been scientifically proven by the competent federal agency, upon registration (Law No. 9,787, of February 10, 1999);

XXVI - generic drug – drug similar to a reference or innovative product, which with it is intended to be interchangeable, usually produced after the expiration or waiver of patent protection or other proprietary rights, its effectiveness, safety and quality are proven, and designated by BCD or, in his absence, by the ICD (Law No. 9,787, of February 10th, 1999);

XXVII - similar drug - one that contains the same active ingredients, has the same concentration, pharmaceutical form, route of administration, dosage and therapeutic indication, and which is equivalent to the drug registered in the federal agency responsible for sanitary surveillance, which may differ only in characteristics related to size and shape of the product, shelf life, packaging, labeling, excipients and vehicles; it must always be identified by its brand or trade name; (Provisional Rule No. 2,190-34, of 2001);

XXVIII - new drug - drug with API not registered in the country, their new salts, isomers or mixtures of isomers, esters, ethers, complexes or other derivatives not registered as well;

XXIX - drug name: the name of the technically prepared pharmaceutical product to distinguish it from other, even though belonging to the same registration holder;

XXX - batch number - designation printed on the label of a drug and products covered by Law No. 6,360, of September 23, 1976, allowing the identification of the batch or numbering system to which they belong and, if necessary, to locate and review all manufacturing operations and inspection practiced during production (Law No. 6,360, of September 23, 1976);

XXXI - bulk product - any product that has undergone all production stages, not including the packaging process. Sterile products in their primary packaging are considered bulk product (RDC No. 17, of April 16, 2010);

XXXII - finished product - a product that has undergone all production stages, including labeling and final packaging (Resolution - RDC No. 17, of 16/04/2010);

XXXIII - intermediate product - partially processed product containing the API and that must be subjected to subsequent manufacturing steps before it becomes a bulk product (Adapted from Resolution - RDC No. 17, of April 16, 2010); and

CHAPTER II

GENERAL PROVISIONS

Article 5 – All documents must be submitted in numbered hardcopy and initialed on all pages.

§ 1 – The documentation must be submitted in accordance with the order established in this Resolution, together with an index containing the numbers of the respective pages thereof.

§ 2 – Registrant must add to the printed documentation a file in PDF format, which allows the performance of text search, and copy with all requirements of the *caput* of this article.

§ 3 – The provisions of the *caput* of this Article shall not apply to cases of electronic submission.

Article 6 – The official documents in foreign language used for registration purposes, issued by the sanitary authorities, must be accompanied by certified translation as provided by law.

Article 7 – For the purposes of this Regulation, in case there is specific legislation or guides, these must be met and their proof must be presented.

Sole paragraph – ANVISA may require, at its discretion and with technical justification, tests and documents to be submitted in cases not provided for in this Resolution, or not conforming to any of the specified requirements.

Article 8 – The batch size to be registered shall be applied to batch used for proof of safety and efficacy demonstrated by pharmaceutical equivalence, bioequivalence and clinical studies, as appropriate.

§ 1 – The batch size to be considered for registration approval of generic and similar drugs must have the batch size used for proof of pharmaceutical equivalence and bioequivalence as reference. Approval for a range of industrial batch size will be permitted provided that all documentation and proof required are submitted pursuant to the specific legislation for post-registration changes in force.

§ 2 – The batch size to be considered for approval of new drug must have the batch size used for proof of safety and efficacy as reference. ANVISA may consider for registration a batch size different from that described in this article, provided that the change history of formulations, production processes, batch sizes, and manufacturing locations held throughout the clinical development and the results of the comparability studies conducted with the drug to be registered are presented.

Article 9 – If the company requests, concurrently to registration, the inclusion of more than one drug manufacturing location or more than one active pharmaceutical ingredient (API) manufacturing location, all additional documentation and proofs required in the in the specific legislation for post-registration changes in force must be submitted.

Sole paragraph – For cases in which the specific legislation for post-registration changes in force requires submission of stability study protocols, the ongoing full accelerated and long-term studies must be presented for purposes of registration.

Article 10 – New and similar drugs must mandatory adopt drug name, in accordance with specific legislation in force.

Article 11 –.Presentations of the drug to be registered must be in accordance with the drug dosage regimen and therapeutic indication.

Article 12 – ANVISA may, at its discretion and with technical justification, require additional evidence of drug quality and may require new studies for quality, safety and efficacy evidence.

§ 1 – ANVISA may ask the company to provide the raw data from clinical and non-clinical trials as well as data quality of the drug.

§ 2 – The requirement of additional evidence may occur even after the registration grant.

Article 13 – In cases arranged in the rule in which registrant is requested to submit the Pharmacovigilance Report or Plan, or Risk Minimization Plan, or Executive Summary for the period of five years from the Periodic Pharmacovigilance Report, the documentation must be filed by means of a petition directed to ANVISA's area responsible for drug pharmacovigilance, after filing the registration or renewal application.

Article 14 – The clinical trial report, when requested, must contain, in addition to the provisions of specific requirements, the following information:

I - references, if available;

II - all available clinical information, favorable and unfavorable to the drug under study;

CHAPTER III

GENERAL REGISTRATION REQUIREMENTS

Section I

Measurements Preceding the Registration of a New Drug

Article 15 – All clinical studies conducted in the country for registration purposes must follow the specific legislation for clinical research in force.

Sole paragraph – Prior approval of the clinical development conducted in the country is mandatory for the use of results for registration purposes.

Article 16 – Registrant shall request to the Brazilian Pharmacopoeia the inclusion of the API and excipient in the Brazilian Common Denomination (BCD) list if this is not already present therein.

Section II

Measurements preceding the Registration of a Generic and Similar Drug

Article 17 – Registrant must consult the reference drug list available on ANVISA website to check if there is an elected reference drug in the concentration and pharmaceutical form for the drug to be registered.

Sole paragraph – In the absence of an elected reference drug, a request for election of a reference drug must be filed at ANVISA, in accordance with specific legislation in force.

Article 18 – The following will not be accepted for registration as a generic or similar drug:

- I - biologics and immunotherapy products derived from human plasma and blood;
- II - herbal medicines;
- III - specific drugs;
- IV - dynamized drugs;
- V - drugs with simplified notification process;
- VI - antiseptics for hospital use;
- VII - products with radiological contrasts and diagnostic purposes;
- VIII - radiopharmaceuticals;
- IX - medical gases; and
- X - other classes of drugs that may have specific legislation for registration.

Section III

Administrative Documentation

Article 19 – The application for drug registration pursuant to this Resolution must be individualized for each pharmaceutical form.

Sole paragraph – The process shall be the same for generic and similar drugs in which there are different elected reference drugs for different concentrations of the same pharmaceutical form.

Article 20 – All filed petitions must be accompanied by the following documents:

- I - application forms, FP1 and FP2, duly completed and signed;
- II - proof of payment of Sanitary Surveillance Inspection Fees-SSIF and respective official fees, or exemption, if applicable;
- III - package leaflet text model;
- IV - layout of the primary and secondary packaging of each presentation of the drug, for each manufacturing location;
- V - copy of a valid Good Manufacturing Practices of Certificate (GMPC) issued by ANVISA for the production line in which the drug to be registered will be manufactured, or copy of the inspection request protocol for purposes of issuance of the GMP certificate; and

§ 1 – If there is more than one manufacturing location or production stages, the documentation described in section V for each company involved in the drug production chain must be presented.

§ 2 – For the cases wherein there is reciprocity between ANVISA and the Regulatory Authority of the country where the drug is manufactured, the proof of good manufacturing practices issued by the agency responsible for Sanitary Surveillance in the manufacturing country may be submitted.

§ 3 – For intermediate products, proof of good manufacturing practices issued by the agency responsible for Sanitary Surveillance in the manufacturing may be submitted.

§ 4 – In the case of imported products, copy of the inspection request protocol for purposes of issuance of the GMP certificate must be accompanied by a copy of the valid document proving good manufacturing practices in pharmaceutical production line issued by the agency responsible of Sanitary Surveillance of the manufacturing country.

§ 5 – The lack of valid GMPC will not prevent the submission of the registration application, but will prevent its approval.

Article 21 – Besides the list of documents contained in article 20 for imported drugs, the phase of the drug to be imported must be informed as a finished product, bulk product or in primary packaging.

Sole paragraph – For a new drug, it must be submitted, when available, information on any commitments to other agencies regarding further evaluation of clinical safety, clinical efficacy, clinical pharmacology or non-clinical toxicology. The presentation of this information will not preclude the submission of the registration application.

Section IV

Quality Technical Documentation

Article 22 – When filing an application for drug registration, registrant must submit a technical report containing the following information:

I - Regarding the active pharmaceutical ingredient (API):

- a) nomenclature: Brazilian Common Denomination (BCD);
- b) structure: structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass;
- c) physical and chemical properties: physical form, stoichiometric relationship between the API chemical form and its pharmacodynamically active component, melting point, solubility, particle size and pKa;

- d) name (s) of the API manufacturer (s) with the corresponding address (es) and document issued by the official sanitary agency of the country of origin proving authorization for the activity of manufacturing API;
- e) description of the synthesis process: flow chart of the synthesis process, including molecular formula, chemical structures of starting materials, intermediates and their nomenclatures, solvents, catalysts, reagents and the API, contemplating the stereochemistry;
- f) elucidation of the structure and other characteristics and impurities: confirmation of structure based on the synthesis route and spectral analysis covering the infrared spectrum of the molecule and other analysis necessary for correct identification and quantification of the molecule (s), and information on structural and geometric isomerism potential, specific optical rotation, refractive index, chirality, potential to form polymorphs, detailing its features and other polymorphs related to the API, and information on impurities;
- g) quality control: specifications, specifications justification for non-pharmacopeial IFA, analytical methods and validation and certificate of analysis from a batch issued by the IFA manufacturer; and
- h) stability: a summary of the types of studies conducted and the results, in accordance with specific legislation in force, including the results of forced degradation and stress conditions studies and the respective analytical procedures, as well as conclusions on the shelf life or retest date and packaging material.

II - regarding the formulation development:

- a) summary of the formulation development, taking into account the route of administration and use, as well as the packaging system;
- b) information on the compatibility of API with the excipients, the main API physicochemical characteristics that can influence on the performance of the finished product;
- c) documents with manufacture, characterization, and control details, with references to support safety data for the excipients used for the first time in a drug or a new route of administration;
- d) data and discussion on evaluating the effectiveness of the preservative system (s) used in the formulation; and
- e) justification in the case of active excess.

III - regarding the finished product:

- a) detailed description of the complete formula, assigning components according to the Brazilian Common Denomination (BCD);
- b) information on the amount of each component of the formula and their respective functions, including the components of the capsule, and details of their references of quality specifications described in the Brazilian Pharmacopoeia or other official codes authorized by the specific legislation in force;
- c) detailed description of the qualitative and quantitative proportion of intermediates used in the formula of the finished product; and
- d) justification for the presence of the groove on the tablet with the proper tests.

IV - regarding the production of the finished product:

- a) production dossier referring to 1 (one) batch;
- b) name and responsibility of each manufacturer including contractors, and each proposed manufacturing location involved in the production and tests to be performed, including quality control and accelerated stability and long-term studies;
- c) flowchart with the manufacturing process steps showing where materials enter the process, identifying the critical points of the process and the checkpoints, intermediate testing and control of the final product;
- d) information on batch sizes of the finished product, description of the manufacturing process steps including all parameters used, process control and intermediate products;
- e) list of equipment involved in the production, identified by principle of operation (class) and design (subclass) with their respective abilities;
- f) control of critical steps with information about the acceptance tests and criteria carried out in critical points identified in the manufacturing process, in addition to the process controls; and
- g) summary report of the manufacturing process validation, including batches, definition of critical manufacturing steps with the respective reasons, assessed parameters, and indication of obtained results and conclusion.

V - regarding the quality control of raw materials:

- a) specifications, analytical methods and analytical report for excipients, accompanied by references made by the drug manufacturer;

- b) additional information for excipients of animal origin in accordance with the specific legislation in force on Transmissible Spongiform Encephalopathy control; and
- c) specifications, analytical methods and analytical report for the active pharmaceutical ingredient, accompanied by references made by the drug manufacturer.

VI - regarding the quality control of the finished product:

- a) specifications, analytical methods and analysis report, accompanied by references, including analytical method validation reports; and
- b) graph of the dissolution profile, when applicable.

VII - regarding the functional primary and secondary packaging:

- a) description of the packaging material; and
- b) report with specifications, analytical method and results of packaging quality control.

VIII - regarding the intermediate wrap: description of the material constituting the intermediate wrap and its specifications;

IX - regarding the accessories accompanying the drug in its commercial packaging: description of the material constituting the accessory and its specifications; and

X - regarding the stability studies of the finished product:

- a) report with the results of accelerated stability and long-term studies conducted with 3 (three) batches, protocols used, including conclusions on the careful conservation and shelf life;
- b) results of stability studies for drugs that, after open or prepared, may be altered in its original shelf life or original careful conservation; and
- c) results of the photostability study or technical justification for the exemption of the study;

§ 1 – The information set forth in item I and its sub items must demonstrate the authenticity of origin of API (s); the manufacture (s) may sent to ANVISA, within thirty (30) days after the registration filing, documentation, such documentation properly identified with the case number to which it relates.

§ 2 – Pursuant to item I, for API registered at ANVISA, the number of the registration process and the API registration number must be submitted, replacing documents of sub items b, e, f and h.

§ 3 – In compliance with sub item g of item I, justifications for specifications of non-pharmacopeial API must be submitted.

§ 4 – In compliance with sub item b of item II, in case of associations, discussion on the compatibility between actives and between these and the excipients must be presented.

§ 5 – Pursuant to item II, for generic and similar drugs, the report showing development of the dissolution method must be submitted according to specific legislation in force.

§ 6 – In compliance with sub item a of item III, in the absence of BCD for any excipient used in the formulation it must be presented justification of absence issued by the Brazilian Pharmacopoeia.

§ 7 – The information set forth in items III and IV and its sub items must be submitted as provided in Annex I.

§ 8 – Pursuant to sub item a of item IV, in cases wherein the registration application refers to more than one concentration, the production dossier must be submitted for highest and lowest concentration, provided that the formulations are qualitatively the same, are proportionate and are manufactured in the same location and with the same production process.

§ 9 – In compliance with sub item c of item V, justification for specifications and analytical methods with respective validations for non-pharmacopoeial API must be presented.

§ 10 – Pursuant to item VI, in addition to the previous paragraphs, companies wishing to import drugs must present methodology and analytical report of physicochemical, chemical, microbiological and biological quality control, and respective validations performed by the importer, according to the finished, bulk or in primary packaging pharmaceutical form.

§ 11 – Pursuant to item IX, the respective registration number for diluent/restorative solution accompanying the drug to be registered must be presented.

§ 12 – In accordance with item IX, in case the diluent/restorative solution has not been registered at ANVISA, the company must submit documentation according to specific legislation in force.

§ 13 – Compliant to item IX, accessory must obligatorily be in adequate quantity and graduation considering its dosage, if applicable.

§ 14 – In relation to the shelf life referred to in sub item a of item X, in the case of imported bulk products, the period shall run from the date of its overseas manufacturing, and not from the date of packaging here in Brazil, respecting the shelf life registered at ANVISA.

CHAPTER IV

SPECIFIC REQUIREMENTS FOR REGISTERING A NEW DRUG

Section I

Registration of a New Drug

Article 23 – This section refers to the registration of drugs with API not registered in the country, their new salts, isomers or mixtures of isomers, esters, ethers, complex or other derivatives, also unregistered.

Article 24 – registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

I - safety and efficacy report according to specific guide, containing:

- a) non-clinical trial report; and
- b) phase I, II and III clinical trial report.

II - Pharmacovigilance plan, according to specific legislation in force.

§ 1 - In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan set forth in item II.

§ 2 – In the case of drugs marketed in other countries, updated Pharmacovigilance Report of the drug must be submitted with the registration application.

Article 25 – The company may exceptionally present the clinical trial report containing concluded phase II studies and initiated phase III studies in order to apply for registration of new drug intended to prevent or treat severe life threatening or highly debilitating diseases, provided that unmet medical need is demonstrated for both cases.

Sole paragraph – In specific cases wherein phase III studies are not applicable and phase II studies are sufficient for proving the efficacy and safety of the drug, the company may submit the registration application after conclusion of phase II studies.

Section II

Registration of a New Association

Article 26 – This section refers to the registration of a new drug composed of a new combination of two or more APIs already registered in the country in:

I - a fixed ratio of doses in the same pharmacotechnical unit hereinafter fixed-dose combination; or

II - a fixed ratio of doses in different pharmaceutical units in the same package, for simultaneous or sequential use, hereinafter kit.

Sole paragraph – In the cases wherein one or more APIs or new salts, isomers or mixture of isomers, esters, ethers, complexes or derivatives of such API (s) comprising the association is (are) not recorded in the country, a registration application for the association shall meet the same requirements provided for the registration of a new drug.

Article 27 – registration of new associations in kit form will be allowed only when:

I - the inability to register a fixed-dose combination in any pharmaceutical form is pharmacotechnically justified, and the kit is clearly beneficial to the public health or

II - the inability to register a fixed-dose combination in any pharmaceutical form is pharmacotechnically justified, and the kit shows increased adherence to treatment and the clinical relevance of this increase has been properly investigated and proven to the target population.

Section III

Registration of a Fixed-Dose New Association

Article 28 – The registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

I - technical justification of the rationality of the association; and

II - safety and efficacy report according to specific guide, containing:

a) non-clinical trials, where applicable;

b) phase I and II clinical trials, where applicable, and phase III studies for each therapeutic indication, proving that:

1. associations with the same API doses have an additive or synergistic effect without increasing the risks when compared to each API alone or with combinations of them with a smaller number of APIs; or

2. association with lower dose of at least one of the APIs obtains the same benefit equal to or smaller risks as compared to an association with known dosages.

III - Pharmacovigilance Plan appropriate to the new fixed-dose association, in accordance with the specific legislation in force.

§ 1 – The efficacy and safety report must include information on the pharmacokinetic and pharmacodynamic interactions between the APIs that make up the association.

§ 2 – In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan referred to in item III.

§ 3 – In the case of drugs marketed in other countries, the upgraded Pharmacovigilance Report of the drug must be submitted.

Section IV

Registration of a New Pharmaceutical Form

Article 29 – This section refers to the registration of new pharmaceutical form in the country for an already registered drug.

Article 30 – The registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

I - technical justification;

II - safety and efficacy report according to specific guide, containing the results of phase III and phase I and II, if applicable, clinical studies; and

III - Pharmacovigilance plan suitable to the new pharmaceutical form, according to specific legislation in force.

§ 1 – Pursuant to item II, phase II and III clinical studies may be replaced by relative bioavailability test when the proposed drug is within the approved therapeutic range.

§ 2 – In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.

§ 3 – In the case of drugs marketed in other countries, the upgraded Pharmacovigilance Report of the drug must be submitted.

Section V

Registration of a New Concentration

Article 31 – This section refers to the registration of a new concentration in the country for a drug registered in the same pharmaceutical form.

Article 32 – The registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

I - technical justification;

II - safety and efficacy report according to specific guide, containing the results of phase III and phase I and II, if applicable, clinical studies; and

III - Pharmacovigilance plan suitable to the new concentration, according to specific legislation in force.

§ 1 – Pursuant to item II, phase II and III clinical studies may be replaced by relative bioavailability test when the proposed drug is within the approved therapeutic range.

§ 2 – In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.

§ 3 – In the case of drugs marketed in other countries, the upgraded Pharmacovigilance Report of the drug must be submitted.

Section VI

Registration of a New Rote of Administration

Article 33 – This section refers to the registration of a new route of administration in the country for an already registered drug in the same pharmaceutical form, same concentration and same therapeutic indication.

Article 34 – The registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

I - technical justification;

II - safety and efficacy report according to specific guide, containing the results of phase III and phase I and II, if applicable, clinical studies; and

III - Pharmacovigilance plan suitable to the new rote of administration, according to specific legislation in force.

§ 1 – Pursuant to item II, phase II and III clinical studies may be replaced by relative bioavailability test when the proposed drug is within the approved therapeutic range.

§ 2 – In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.

§ 3 – In the case of drugs marketed in other countries, the upgraded Pharmacovigilance Report of the drug must be submitted.

Section VI

Registration of a New Therapeutic Indication

Article 35 – This section refers to the registration of a new therapeutic indication in the country for an already registered drug in the same pharmaceutical form and same concentration.

Article 36 – The registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

- I - technical justification for the registration;
- II - safety and efficacy report according to specific guide, containing the results of phase III and phase I and II, if applicable, clinical studies; and
- III - Pharmacovigilance plan suitable to the new therapeutic indication, according to specific legislation in force.

§ 1 – In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.

§ 2 – In the case of drugs marketed in other countries, the upgraded Pharmacovigilance Report of the drug must be submitted.

Section VIII

Registration of a Drug with the same API (s) of an already Registered New Drug

Article 37 – This section refers to the registration of a drug in case there is an already registered new drug with the same API (s).

Sole paragraph – The provisions of the *caput* of this Article shall not apply to drugs classified as generic and similar for which there is technical feasibility for conducting pharmaceutical equivalence and the relative bioavailability (bioequivalence) study for proving efficacy and safety of the drug.

Article 38 – registration petition described in this section, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by:

- I - technical justification for the registration;
- II - Safety and Efficacy report according to specific guide, containing:
 - a) non-clinical trial report;
 - b) phase I, II and III clinical trial report
- III - Pharmacovigilance plan according to specific legislation in force.

§ 1 – In specific safety-related situations, a Risk Minimization Plan may be required in addition to the Pharmacovigilance Plan.

§ 2 – In the case of drugs marketed in other countries, the upgraded Pharmacovigilance Report of the drug must be submitted.

Section X

Relative Bioavailability Studies

Article 39 – For the registration of a new drug for which is necessary to present relative bioavailability studies pursuant to this Resolution, addition to the studies according to the guidelines available on ANVISA website shall be submitted.

CHAPTER V

SPECIFIC REQUIREMENTS FOR REGISTERING A GENERIC AND SIMILAR DRUG

Section I

Article 40 – The petition requesting registration of similar and generic drugs, in addition to the documentation cited in Sections III and IV of Chapter III, must be accompanied by a pharmaceutical equivalence certificate and dissolution profile certificate and report showing the development of the dissolution method, in accordance with specific legislation in force.

Sole paragraph – This Article shall not apply if the manufacture of generic or similar drug and the reference drug is made in the same manufacturing location, with identical formulation, production process and equipment.

Section II

Bioequivalence Studies

Article 41 – For the registration of similar and generic drugs, in addition to the documentation cited in Sections III and IV of Chapter III, addition to the bioequivalence studies according to the guidelines available on ANVISA website shall be submitted.

Article 42 – bioequivalence study or bioisention tests must necessarily be performed with the same batch used in pharmaceutical equivalence study.

CHAPTER VI

REGISTRATION RENEWAL

Article 43 – For purposes of registration renewal of a drug at ANVISA, all companies in the first half of the last year of the five-year period of validity of an already granted registration, must submit:

- I - application forms, FP1 and FP2, duly completed and signed;
- II - proof of payment of the Sanitary Surveillance Inspection Fee-SSIF and respective official fees, or exemption, if applicable;
- III - executive summary in Portuguese for the period of five years from the Periodical Pharmacovigilance Report of the same period; and

IV - document proving sales in the last five years of the registration term containing the invoice numbers issued in Brazil and the list of buyer establishments at a minimum of 1 (one) invoice issued in the country, by pharmaceutical form and concentration.

Sole paragraph – In the case of official laboratories, justification for non-marketing must be presented when there is no production of the drug in the period referred to in item IV.

CHAPTER VII

TRANSITORY AND FINAL PROVISIONS

Article 44 – During the analysis of the registration or renewal process, the drug manufacturer may be audited at the discretion of ANVISA.

Article 45 – information with the technical bases for approval of drug registration will be disclosed on ANVISA website.

Article 46 – ANVISA may issue technical guidance on the applicability of this Resolution to specific cases of drug registration, such as the presentation of data to prove safety and efficacy for incremental innovations in cases those are necessary.

Article 47 – Noncompliance with the provisions of this Resolution constitutes a sanitary violation, pursuant to Law No 6,437, dated August 20, 1977, without prejudice to the civil, administrative and criminal liabilities.

Article 48 – Resolution – RDC No. 136, of May 29, 2003; Resolution – RDC No. 16, of March 2nd, 2007, except for items 1 and 2, VI, of Annex I; Resolution – RDC No. 17 of March 2nd, 2007, except for items 1 and 2, VI, of Annex; 1st and 4th Articles of Resolution – RDC No. 210, of September 2nd, 2004; and Section I and II of Chapter XVIII of Resolution – RDC No. 48, of October 6th, 2009.

Article 49 – Registration applications for new, generic and similar drugs filed prior to the publication date of this resolution, or that are already under analysis at the General Drug Management, shall be analyzed in accordance with the resolutions in force at the filing date.

Article 50 – This Resolution shall enter into force within 90 (ninety) days counted as from its publication date.

DIRCEU BRÁS APARECIDO BARBANO

Director-President