Agência Nacional de Vigilância Sanitária[1]

www.anvisa.gov.br

Draft Resolution nº 56 of 13 September 2006.
D.O.U.[2] of 14/09/2006.

The Board of Directors of the Agência Nacional de Vigilância Sanitária, in exercise of the powers conferred on it by Art. 11 (IV) and Art. 35 of the ANVISA Regulations, as approved by Decree nº 3029, of 16 April 1999, and having regard to the provisions of Art. 54 (V) (1) and (3) of the Internal Regulations approved pursuant to Annex 1 to ANVISA Order nº 354, of 11 August 2006, republished in the D.O.U. of 21 August 2006, at a meeting held on 4 September 2006,

adopts the following Draft Resolution and I, as Director-Chairman, order the publication thereof:

Art. 1: There is established a period of 45 (forty-five) days from the date of publication of this Draft Resolution for the submission of criticisms and suggestions relating to the updating and adjustment of Resolution (RDC) nº 133, of 29 May 2003, on the Registration of Similar medicines with reference to pharmaceutical manufacturers' documentation and including the Draft Relative Bioavailability Study for contraceptives, endogenous hormones, cyclosporine and mycophenolate mofetil, annexed hereto.

Art. 2: Interested parties are informed that the proposal will be available for inspection in full during the consultation period at http://www.anvisa.gov.br and that suggestions should be sent in writing to the following address: Agência Nacional de Vigilância Sanitária, SEPN 511, Bloco "A" Ed. Bittar II, Asa Norte, Brasília, DF, CEP 70.750.541, by fax on (061)3448-1204 or by e-mail to similares@anvisa.gov.br.

Art. 3: On the expiry of the period stipulated in Art. 1, the Agência Nacional de Vigilância Sanitária will liaise with the Authorities and Entities involved and any others that have expressed an interest in the subject, to enable them to appoint representatives in the subsequent discussions, with a view to consolidating the final text.

DIRCEU RAPOSO DE MELLO

ANNEX

RESOLUTION (RDC) Nº xxx, OF xx xxx 2006

On the registration of similar medicines and laying down other provisions.

The Board of Directors of the Agência Nacional de Vigilância Sanitária, in exercise of the powers conferred on it by Art. 11 (IV) of the ANVISA Regulations, as approved by Decree nº 3029, of 16 April 1999, together with Art. 111 (I) "b" (1) of the Internal Regulations approved by Order nº 593, of 25 August 2000, republished, 22 December 2000, at a meeting held on 6 March 2003,

having regard to Law nº 6360, of 23 September 1976, laying down provisions on the surveillance of medicines, drugs, pharmaceutical raw materials and related substances, cosmetic, medicinal and other products;

having regard to Temporary Measure nº 2190-34, of 23 August 2001, amending Law nº 6360 defining similar medicines;

whereas it is the institutional purpose of ANVISA, in the context of the pharmaceutical market, to ensure that drugs have appropriate guarantees as to safety, effectiveness and quality;

having regard to Decree nº 3961, of 10 October 2001, amending Decree nº 79,094, of 5 January 1977, updating definitions of similar medicines, reference medicines and generic medicines;

having regard to the National Medicines Policy guidelines laid down by Ministry of Health Order nº 3916/98, as regards health regulations, the promotion of production from the pharmaceutical-economic point of view, and the sensible promotion of medicines;

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[1] Brazilian Healthcare Supervisory Agency
[2] Diário Oficial da União / Brazilian Official Journal

adopts the following Resolution and I, the Director-Chairman, order the publication hereof:

Art. 1 To approve the Technical Regulations for the registration of similar medicines, as annexed hereto.

Art. 2 To order that, in order to register a Similar Medicine, companies affected must comply with the provisions of this Regulation.

Art. 3 To order that only laboratories authorised by ANVISA may carry out pharmaceutical equivalence (REBLAS) tests and only laboratories certified by ANVISA may carry out the Relative Bioavailability tests required by this Regulation.

Art. 4 RDC Resolution nº 133, of 29 May 2003, is hereby repealed.

Art. 5 This Resolution shall enter into force on the date of publication hereof.

DIRCEU RAPOSO DE MELLO

ANNEX

TECHNICAL REGULATIONS FOR SIMILAR MEDICINES

SCOPE

These Regulations lay down criteria for the registration of Similar Medicines.

COMPOSITION

These Regulations are composed of three parts: pre-registration measures, legal and technical requirements for registration and post-registration measures.

Technical details for implementation and compliance with the relevant legal requirements relating to registration, and any amendments and additions thereto, will be set out in official guidelines according to subject-matter.

DEFINITIONS

RELATIVE BIOAVAILABILITY - The quantity and rapidity quotient of an active principle that enters the systemic circulation by means of the extra-vascular administration of a preparation and the quantity and rapidity quotient of an active principle that enters the systemic circulation by means of the extra-vascular administration of a reference product containing the same active principle.

QUALITY CONTROL: A combination of measures designed to ensure the production at all times of batches of medicines and other products governed by this Law that satisfy the requirements of activity, purity, effectiveness and harmlessness;

DENOMINAÇÃO COMUM BRASILEIRA[3] (DCB) - the name of the pharmaceutical or active principle approved by the Federal authority responsible for the supervision of healthcare;

INTERNATIONAL NONPROPRIETARY NAME (INN) - the name of the pharmaceutical or active principle approved by the World Health Organisation;

PHARMACEUTICAL EQUIVALENTS: medicines that contain the same pharmaceutical, that is to say the same salt or ester having the same therapeutically active molecule, in the same quantity and pharmaceutical form, whether or not it contains identical excipients. They must meet the same current specifications of the *Farmacopeia Brasileira*[4] or, if there are none, those of other codes authorised by current legislation, or other applicable quality standards, relating to identity, dose, purity, potency, uniformity of content, disintegration time and dissolution speed, where applicable.

MANUFACTURE: All operations that are necessary to produce the products governed by this Law;

[3] Brazilian nonproprietary name
[4] Brazilian Pharmacological Standards

PHARMACEUTICAL FORM: Final state of presentation of pharmaceutical active principles after one or more pharmaceutical operations carried out with the addition of appropriate excipients or without the addition of excipients, with the object of facilitating the use thereof and obtaining the desired therapeutic effect, with characteristics appropriate to a specific method of administration.

FORMULA - Quantitative list of pharmaceutical chemicals used to make up a medicine.

BATCH OR CONSIGNMENT: Quantity of a medicine or product governed by this Law, produced in a single manufacturing cycle and having the essential characteristic of homogeneity;

RAW MATERIALS: Active or inactive substances used in the manufacture of medicines and other products governed by this Law, whether they remain unaltered or are capable of being modified;

SIMILAR MEDICINE - one that contains the same or similar active principles, has the same concentration, pharmaceutical form, method of administration, dosage and therapeutic instructions, and is equivalent to a medicine registered with the Federal authority responsible for the supervision of healthcare, differing only as regard the characteristics of size and form of the product, period of validity, packaging, labelling, excipients and vehicle. It must always be identified by a commercial name or trade mark;

BATCH NUMBER: An indication printed on the label of a medicine or product governed by this Law that makes it possible to identify the batch or consignment to which it belongs and, where necessary, to locate and review all the manufacturing and inspection operations carried out in the course of production;

REBLAS - Rede Brasileira de Laboratórios Analíticos em Saúde.[5]

I - MEASURES TO BE TAKEN PRIOR TO THE REGISTRATION OF SIMILAR MEDICINES

Before submitting an application for registration of a product as a Similar Medicine, applicants must formally:

1. Consult the list of reference medicines available on the ANVISA website to check whether there are any details, as to pharmaceutical concentration and form, of the product intended to be registered as similar. If there is none, the applicant should send a formal application to ANVISA requesting details of the reference medicine, submitting the following information, as to both the test medicine and the Reference Medicine specified: company, product, active principle, pharmaceutical form, concentration and proof of the sale/distribution in Brazil of the medicine specified as a reference.

2. Apply to ANVISA for a medicine import licence (LI) for *in vitro* and *in vivo tests*, where appropriate.

3. Submit a Pilot Batch Production Notice as prescribed by the GUIDELINES FOR GIVING NOTICE OF PILOT BATCHES OF MEDICINES, where appropriate.

4. In order to register contraceptives, endogenous hormones, cyclosporine and mofetil mycophenolate, in pharmaceutical forms not exempt from the Relative Bioavailability study requirement, the company must submit a Draft Relative Bioavailability Study carried out by an ANVISA-certified laboratory, in accordance with the Guidelines for the Preparation of Relative Bioavailability/Bioequivalence studies, except for studies commenced before the date of publication of this Resolution. The study timetable must be annexed to the draft, and ANVISA must be informed of any alteration. The timetable must be capable of being verified *in situ* at ANVISA's discretion

4.1 For other medicines, the company will be authorised to submit the draft Relative Bioavailability Study.

5. During the examination of the registration process, the company manufacturing/producing the medicine, the laboratory responsible for the pharmaceutical equivalence study and the laboratory responsible for the Relative Bioavailability study may be inspected at ANVISA's discretion.

II - REGISTRATION

1. The application process for the registration of similar medicines must consist entirely and exclusively of the documentation described below. The company must have complied with the pre-registration formalities and must submit the following documents:

[5] Brazilian Network of Laboratories for the Analysis of Healthcare Products.

a) Application forms FP1 and FP2, duly completed;

b) Original proof of payment of the healthcare supervision administration fee, or exemption where applicable;

c) Copy of current Operator's Licence (Alvará Sanitário) of the company manufacturing or producing the medicine;

d) Current Certificate of Technical Responsibility, issued by the Regional Pharmacy Council;

e) Proof of issue of notice of production of pilot batches;

f) Draft instructions for use of the medicine and layout of its primary and secondary packaging, in accordance with specific legislation.

- f.1) Information contained in the instructions for use of the similar medicine must not be inferior to that contained in the instructions for use of the reference medicine. Anvisa reserves the right to require the addition of further data wherever there is a technical recommendation. A copy of the instructions for use of the reference medicine currently sold must be annexed.
- f.2) With regard to instructions for the use of medicines produced by official pharmaceutical laboratories, these must comply with specific regulations.
- f.3) Where medicines are presented in drops (oral and ophthalmic solutions, oral emulsions and oral, nasal and ophthalmic suspensions), the number of drops corresponding to 1 ml must be determined, and the concentration per ml of the pharmaceutical must be indicated.
- f.4) With regard to the packaging of medicines produced by official pharmaceutical laboratories, this must comply with specific regulations.

g) Results of accelerated stability studies of three pilot batches used in the tests, together with long-term stability studies in progress or long-term stability studies already completed in accordance with the GUIDELINES FOR MEDICINE STABILITY STUDIES. For medicines with three or more concentrations and proportional preparation formulae, the results of the stability study of the lesser and greater concentrations must be submitted.

h) The results of pharmaceutical equivalence tests must be submitted for all medicines, describing the method used, by authorised laboratories (REBLAS), in accordance with the GUIDELINES FOR PHARMACEUTICAL EQUIVALENCE STUDIES AND PREPARATION OF REPORTS.

i) Report on Relative Bioavailability tests for medicines sold on prescription and not exempt from this study, carried out at an ANVISA-certified laboratory. The stability of the batches used must have been proved and the batches must have been produced in equipment intended to be used for industrial-scale production. The relative bioavailability study must conform to the GUIDELINES FOR DESIGNS APPLICABLE TO BIOEQUIVALENCE STUDIES. Companies shall be authorised to submit drafts of their Relative Bioavailability Studies. The results must be submitted in accordance with the GUIDELINES FOR THE PREPARATION OF TECHNICAL REPORTS ON RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE STUDIES.

- i.1) Medicines exempt from this study are listed in the GUIDELINES FOR EXEMPTION FROM AND REPLACEMENT OF BIOEQUIVALENCE STUDIES. In the case of oral preparations for immediate release with a highly soluble active principle or principles, high intestinal permeability and a wide therapeutic window, already released from the requirement of proof of relative bioavailability by the United States (FDA) and European (EMEA) regulatory authorities, documentary evidence of that exemption must be included.
- i.2) Where the pharmacokinetic parameters (C max., AUC and T max.) between the test medicine and the reference medicine indicate that an adjustment is required, the preparation formula of the product may be altered until they are compatible. A company that opts not to change the preparation formula must suggest a dosage that ensures safety and effectiveness where the pharmacokinetic curves are below the safety limit and above the therapeutic limit. In any such case, the medicine will be a product of the alteration of pharmacokinetic properties, will be exempt from the submission of a clinical study and cannot be a reference product.
- i.3) In the case of a Similar Medicine composed by means of a combination of medicines, or two or more presentations in a single pack for simultaneous or successive use, the relative bioavailability of each active principle in relation to the reference medicine must be proved.

j) Compete production reports:

- j.1) pharmaceutical form;
- j.2) detailed description of the complete formula, describing the components in accordance with their CBN or CIN or the name described in the CAS, in that order of priority;

j.3) description of the quantity of each express substance in the international unit system (IS) or standard unit, indicating its function in the formula;
j.4) minimum and maximum sizes of the industrial batches to be produced;
j.5) description of all stages of the production process including the equipment used;
j.6) Copies of complete production and quality control files, including order of production, detailed production process and controls during the process, relating to the three pilot batches manufactured, the Notice of Production of which has previously been submitted prior to the registration application. For Brazilian medicines already registered in Brazil and imported medicines, the production file must relate to three industrial batches manufactured in the last three years. In the case of medicines with three or more concentrations and proportional formulae, files for the lesser and greater concentration must be submitted.

k) Complete quality control reports on all raw materials used and on the medicine; the specification should be submitted together with the bibliographical reference of the pharmacological standards manual consulted, and recognised by ANVISA, in accordance with current legislation. Where no official compendium recognised by ANVISA is used, specifications should be submitted together with a detailed description of all quality control methods used and duly validated analytical methods for the active principle(s) and the medicine, in accordance with the GUIDELINES FOR THE VALIDATION OF ANALYTICAL AND BIOANALYTICAL METHODS, indicating the bibliographical or development source. In the latter case a translation should be submitted where the language is not English or Spanish.

With regard to pharmaceuticals, applicants must indicate which manufacturer is being used in the batch of medicine submitted for pharmaceutical equivalence and relative bioavailability and must send copies of the original documents listed below supplied by the companies that manufacture the pharmaceuticals, on paper bearing the letterhead of the producing company:

k.1) general details of the manufacturing company with full address of the premises where the pharmaceutical is manufactured;
k.2) synthetic rota, with description of the intermediate molecules, their chemical names and solvents used;
k.3) description of the manufacturer's specifications;
k.4) identification and analytical methods used by the manufacturer;
k.5) quantification and limits of the principal contaminants, according to the synthetic rota of the pharmaceutical;
k.6) data on ester isomer content, in the case of pharmaceuticals that show chirality, in which the ester isomer proportions may endanger the effectiveness and safety of the medicine;
k.7) information on and definition of probable polymorphs and analytical methods used for polymorphic pharmaceuticals;
k.8) validation of analytical methods used, where other than those recommended by the pharmacological standards manual;
k.9) Copy of the analytical quality control report supplied by the manufacturer of the pharmaceutical;
k.10) where more than one pharmaceutical manufacturer is submitted, the following documentation must be submitted in addition to the items listed above for any manufacturer(s) not subject to pharmaceutical equivalence and relative bioavailability requirements:
  k.10.1) results and evaluation of an accelerated stability study of the batch of medicine produced for each manufacturer represented, in accordance with the GUIDELINES FOR STABILITY STUDIES;
  k.10.2) analytical report on the medicine in accordance with the specifications and methods submitted during the registration process for each manufacturer.
  k.10.3) for solid pharmaceuticals, comparative dissolution profile between the medicine submitted for the bioavailability and pharmaceutical equivalence studies and the medicine produced by each manufacturer;

l) Specifications of the primary packaging material. Where a dropper is involved, routine analytical tests and methods should be submitted;

m) Additional information, in accordance with the current legislation on the control of Transmissible Spongiform Encephalopathy, should be sent where appropriate.

n) Certificate of Correct Manufacturing and Control Practice (CMCP) issued by ANVISA, for the production line on which the product classified as a similar medicine will be manufactured, or a copy of the inspection application form for the purposes of issue of the CMCP certificate. This form will be valid provided that the proposed production line is satisfactory on the final inspection for the purposes of verification of due compliance with CPBF.

2. In addition to the items aforementioned, manufacturers or their representatives intending to sell similar medicines produced abroad and imported in bulk, in their primary packaging or as a finished article, must submit the following:

a) Licence held by the manufacturing company for the registration, commercial representation and use of the mark in Brazil, where appropriate.

b) Copy of the current CMCP Certificate issued by ANVISA for the manufacturing company, for each production line

b.1) Where ANVISA has not yet carried out an inspection at the premises of the manufacturing company, proof of an application to ANVISA for a health inspection will be accepted if accompanied by a certificate of correct pharmaceutical manufacturing practice for each production line, issued by the authority responsible for Healthcare Supervision in the country of manufacture.

c) Proof of registration of the medicine, issued by the authority responsible for Healthcare Supervision in the country of manufacture. If this is impossible proof of current registration, issued by the authority responsible for Healthcare Supervision in the country in which the medicine is sold or by an international health authority, must be submitted.

d) Physical-chemical, chemical, microbiological and biological quality control methods to be used by the importer, according to the pharmaceutical form of the bulk product, on the primary or final packaging. If the method is not found in the pharmacological standards manual, validation of the analytical methods must be sent.

e) A copy of a current Certificate of Correct Manufacturing and Inspection Practice issued by ANVISA for the manufacturing company's production line should be submitted where the product is imported in bulk, or in its primary packaging.

f) For pharmaceuticals imported in bulk, on the primary or final packaging, the results and evaluation of the stability test on the final sale packaging must conform to the GUIDELINES FOR STABILITY STUDIES OF MEDICINES. A copy of the original results of that study should be sent, together with a translation. Should it be necessary to import samples, an application must be made to ANVISA for the appropriate import licence.

g) The validity period for products imported in bulk should be calculated from the date of manufacture of the product abroad and not the date of packaging in Brazil, in accordance with the validity period registered with ANVISA.

h) All material on the product file, such as production and quality control reports, information contained on labels, in instructions for use and on packaging, must be in Portuguese, in accordance with current legislation. Official documents in foreign languages used for purposes of registration, issued by health authorities, must be accompanied by sworn translations as required by law.

3. Similar medicines may be manufactured simultaneously on more than one site. This possibility is subject to the submission of all the appropriate registration documentation for each manufacturing site, together with technical support for the application and a declaration of official ratification of the service signed by the legal representatives and technical managers of the companies involved. *In vitro* and *in vivo* studies of the medicine must be carried out at each manufacturing site in accordance with the criteria defined in the GUIDELINES FOR THE AMENDMENT, INCLUSION, NOTIFICATION AND CANCELLATION OF MEDICINES AFTER REGISTRATION, and where applicable a comparison of dissolution profiles. The manufacturing site to which the relative bioavailability study relates should be used as a reference.

4. Similar Medicines must adopt a commercial name or trade mark, save in those cases provided for in specific legislation. Such products are legally non-interchangeable. Names must be created in accordance with specific legislation.

5. All documents must be sent in printed form, signed on the final page and initialled on all pages by a technical manager on behalf of the company. Copies of all technical reports on diskette or CD-ROM should be added, with files in file.doc format or any other format accepted by ANVISA.

6. ANVISA may, at any time and at its own discretion, call for additional proof of identity and quality of components of a medicine and/or further evidence to prove its relative bioavailability or pharmaceutical equivalence, should any facts occur that require further evaluation, even after registration has been granted.

7. Multiple-dose liquid and semi-solid pharmaceutical forms for intra-vaginal use must be accompanied by the appropriate measuring accessories, in sufficient quantities for the administration of the medicine.

III - POST REGISTRATION MEASURES

1. Any amendments to the register must be made in accordance with the specific procedures laid down in the GUIDELINES FOR THE AMENDMENT, INCLUSION, NOTIFICATION AND CANCELLATION OF MEDICINES AFTER REGISTRATION.

2. ANVISA may analyse the control of batches sold for the purpose of monitoring the quality of the medicine and its conformity with that registered.

3. Where registration has been granted subject to a provisional validity period, in accordance with the accelerated stability study, on the expiry of the validity period indicated for the medicine the company must submit, on the additional process information form, a report on the results and final evaluation of the long-term stability study of the three batches submitted with the application.

4. All companies must submit the following documents for renewal in the first half of the final year of the five-year validity period of a registration previously granted:

a) Application Forms FP1 and FP2, duly completed;

b) Original proof of payment of the healthcare supervision administration fee, or exemption where applicable;

c) Current Certificate of Technical Responsibility, issued by the Regional Pharmacy Council;

d) Documentary evidence of sale during the registration period, tax return numbers and list of establishments to which sales were effected, with a maximum of 3 (three) declarations per pharmaceutical form and concentration. A declaration may be submitted relating to commercial versions not placed on the market, where the company has an interest in maintaining their registration, provided that at least one version of that pharmaceutical form and concentration has been marketed. Proof of exportation may also be submitted in the case of products exclusively registered for that purpose. Where a medicine is not produced within the said period the Official Laboratories must produce proof that it has not been placed on the market.

e) Latest version of printed instructions for use accompanying the commercial packaging of the product.

f) Copy instructions for use of the medicine chosen as a reference.

g) List of any post-registration amendments and/or additions that have occurred during the last registration validity period for the product, accompanied by D.O.U. copy or, where none exists, copy(-ies) of the relevant application form(s).

h) For imported products, the appropriate physical-chemical, chemical, microbiological and biological quality control reports on the batches imported during the last three years by the importer in Brazil should be submitted according to pharmaceutical form.

i) Production and quality control reports as described in items "j" and "k" for the registration of similar medicines.

j) Results of pharmaceutical equivalence tests, describing the methods used, by authorised laboratories (REBLAS), in accordance with the GUIDELINES FOR PHARMACEUTICAL EQUIVALENCE AND DISSOLUTION STUDIES AND PREPARATION OF REPORTS. These must be accompanied by dissolution profiles where appropriate.

k) Results of long-term stability studies, should the study on the registration file conflict with the GUIDELINES FOR MEDICINE STABILITY STUDIES.

l) Any additional documents required by the legislation on the conformity of medicines already registered.