National Health Surveillance Agency www.anvisa.gov.br

Public Consultation No. 57 of 13 September 2006.
D.O.U. (Official State Gazette) of 14/09/2006.

The Board of the National Health Surveillance Agency, in the exercise of the powers granted by Item IV of Article 11 and Article 35 of ANVISA's Regulations, approved by Decree No. 3029 of 16 April 1999, and having regard to the provisions of Item V and points 1 and 3 of Article 54 of the Internal Regulations approved in accordance with Appendix I of ANVISA Administrative Ruling No. 354 of 11 August 2006, republished in the DOU of 21 August 2006, at a meeting held on 4 September 2006,

agreed to invite the following Public Consultation, and I, the Chief Executive Officer, ordered that it should be published:

Art. 1. A period of 45 (forty-five) days is to commence on the date of publication of this Public Consultation, for the submission of comments and suggestions relating to the proposal to revise RDC Resolution No. 135 of 29 May 2003, concerning the Technical Regulation of Generic Medicines to allow the registration of generic oral contraceptive medicines and oral endogenous hormones, and the inclusion of the Relative Bioavailability Study Protocol for contraceptives, endogenous hormones, cyclosporine and mycophenolate mophetil, which is attached.

Art. 2. To announce that the full proposal will be available, during the consultation period, at the following web site 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 or to Fax: (061)3448-1213 or E-mail: gemeg@anvisa.gov.br.

Art. 3. At the end of the period specified in Art. 1, the National Health Surveillance Agency will talk to the Bodies and Entities involved and other parties with an interest in the matter, and ask them to nominate representatives for subsequent discussions, in order to arrive at a final wording.

DIRCEU RAPOSO DE MELLO

APPENDIX

RDC RESOLUTION NO. XXX, of XXXX, 2006

The Board of the National Health Surveillance Agency, in the exercise of the powers granted to it by Art. 11, Item IV, of the ANVISA Regulations, approved by Decree No. 3029 of 16 April 1999, in accordance with Art. 111, Item I, sub-item "b", point 1 of the Internal Regulations approved by Administrative Ruling No. 593 of 25 August 2000, republished on 22 December 2000, at a meeting held on 6 March 2003,

having regard to Law No. 6360, of 23 September 1976, and its Regulations, approved by Decree No. 79094, of 5 January 1977, which establishes the legal bases for the granting of medicine registrations;

having regard to Law No. 9787, of 10 February 1999, which establishes the legal bases for the establishment of generic medicines in the Country;

having regard to the fact that the same Law, Article 2, provides that it shall be regulated by the federal body responsible for health surveillance;

having regard to the fact that generic medicines in the Country are a priority of the medicines policy of the Ministry of Health;

having regard to the need to ensure the quality, safety and efficacy of generic medicines and to ensure their interchangeability with the corresponding reference products,

agreed the following Resolution, and I, the Chief Executive Officer, ordered that it should be published:

Art. 1. To approve the Technical Regulations for generic medicines, Appendix I.

Art. 2. Companies interested in registering generic medicines must comply entirely with the provisions of these Regulations.

Single paragraph. For the purposes of the provisions of these Regulations, companies must be guided by the technical procedures described in specific guides approved by the Board and published in the Diário Oficial da União (DOU).

Art. 3. Only centres authorised by ANVISA may carry out pharmaceutical equivalence and relative bioavailability/bioequivalence tests.

Single paragraph. Companies interested in carrying out the tests must arrange to register with ANVISA and comply with the legal requirements relating to their activity.

Art. 4. RDC Resolution No. 135 of 29 May 2003 is hereby repealed.

Art. 5. This Resolution shall take effect on the date of its publication.

DIRCEU RAPOSO DE MELLO

APPENDIX I

TECHNICAL REGULATIONS FOR GENERIC MEDICINES

Scope

These Regulations are intended to establish technical rules and procedures for the registration of generic medicines in Brazil, described in the following items.

I. Definitions used for the registration of generic medicines.

II. Measures prior to registration.

III. Documentation for registration.

IV. Medicines which will not be accepted as generic.

V. Post-registration measures.

VI. Criteria for the prescription and dispensing of generic medicines.

These Regulations are accompanied by Appendix II entitled “Cover sheet of the generic medicines registration and post-registration process”.

The definition of technical procedures for the purpose of executing and observing the legal requirements relating to registration and post-registration is contained in specific guides, published in the DOU.

I – Definitions used for the registration of generic medicines.

1. Bioavailability: "indicates the speed and extent of absorption of an active principle in a form of dosage, as measured by the concentration/time in the system circulation curve, or its excretion in the urine (Law No. 9787 of 10/2/99).

2. Common Brazilian Denomination (CBD): “denomination of the drug or pharmacologically active principle approved by the federal body responsible for health surveillance". (Law No. 9787, of 10/2/99)

3. Common International Denomination (CID): "denomination of the drug or pharmacologically active

principle recommended by the World Health Organisation (Law No. 9787 of 10/2/99).

4. Therapeutic equivalence: two medicines are considered therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects in terms of efficacy and safety are essentially the same, as determined by means of appropriate bioequivalence studies, pharmacodynamic trials, clinical trials or *in vitro* studies.

5. Pharmaceutical equivalents: are medicines which contain the same drug, that is, the same salt or ester of the same therapeutically active molecule, in the same pharmaceutical quantity and form, and may or may not contain identical excipients. They must satisfy the same updated specifications in the *Farmacopéia Brasileira* (Brazilian Pharmacopeia) and, if these do not exist, those of other codes authorised by current legislation, or, failing this, of other applicable quality standards relating to the identity, dosage, purity, strength, content uniformity, disintegration time and speed of dissolution, as the case may be.

6. Medicine: "a pharmaceutical product, obtained or prepared by technical means, for prophylactic, curative, palliative or diagnostic purposes". (Law No. 5991, of 17/12/73). It is a pharmaceutically complete form which contains the drug, generally in association with pharmotechnical aids.

7. Bioequivalent medicines: are pharmaceutical equivalents which, when administrated in the same molar dose, under the same experimental conditions, do not exhibit any statistically significant differences in relation to bioavailability.

8. Reference medicine: "an innovative medicine registered with the federal body responsible for health surveillance, and sold in the Country, the efficacy, safety and quality of which were scientifically proved to the relevant federal body, at the time of registration (Law No. 9787 of 10/2/99).

9. Generic medicine: "a medicine similar to a reference or innovative product, which is claimed to be interchangeable with it, generally produced after the expiry or waiver of patent protection or other exclusivity rights, the efficacy, safety and quality of which have been proven, designated by the CBD or, failing this, by the CID". (Law No. 9787 of 10/2/99)

10. Innovative medicine: a medicine sold in the national market composed of at least one active drug, which drug must have been the subject of a patent, even if it has now expired, by the company responsible for its development and introduction into the market in the country of origin. In general, an innovative medicine is considered to be a reference medicine, but if one does not exist, Anvisa will state the reference medicine.

11. Similar medicine: "one containing the same active principle(s), in the same concentration, pharmaceutical form, form of administration, posology and therapeutic indication, and which is equivalent to the medicine registered with the federal body responsible for health surveillance, and may differ only in characteristics relating to the size and form of the product, expiry date, packaging, labelling, excipients and vehicles, and must always be identified by a commercial name or brand. (Wording provided by MP 2190-34, of 23 August 2001)" (Law No. 9787, of 10/2/99)

II – Measures prior to registration

a) Before applying to register the generic medicine, the company concerned must:

1. check the list of reference medicines available on the ANVISA portal to see whether one exists in the concentration and pharmaceutical form for the product it wishes to register as generic. If it does not, it must apply to Anvisa for an indication of the reference medicine, supplying the following details, of both the test medicine and the assumed reference medicine: company; product; active principle; pharmaceutical form; concentration and proof of sale/distribution in Brazil of the medicine cited as the reference.

2. apply for an import licence (IL) for the medicine from ANVISA to carry out trials *in vitro* and *in vivo*, when appropriate.

3. submit a Notification of Pilot Batch Production as provided in the GUIDE FOR THE NOTIFICATION OF PILOT-BATCHES OF MEDICINE, when appropriate.

4. for the registration of contraceptives, endogenous hormones, cyclosporine and micophenolate mophetil, in pharmaceutical forms not exempt from bioequivalence studies, the company must submit

5.
A bioequivalence study protocol, prepared by a Centre certified by the ANVISA, in accordance with the Guide for the Preparation of a Relative Bioavailability/Bioequivalence Protocol, except for studies begun prior to the date of publication of this Resolution. The timetable for carrying out the study must be attached to the

protocol, and ANVISA must be informed of any changes. This timetable is to enable verification *in loco* at ANVISA's discretion.

4.1. For other medicines, the company will be allowed to present the bioequivalence study protocol.

5. During the analysis of the registration process, the manufacturer/producer of the medicine, the centre responsible for the pharmaceutical equivalence study and the centre responsible for the bioequivalence study may be inspected at ANVISA's discretion.

III – Registration documentation

a) manufacture of the generic medicine simultaneously in more than one centre is permitted. This possibility is conditional on the submission, for each manufacturing centre applied for, of all the necessary registration documentation, also the technical justification for the request and a declaration of commitment to provide the service signed by the legal representatives and technical heads of the companies involved. *In vitro* and *in vivo* studies must be carried out for the medicine from each manufacturing centre in accordance with the criteria in the GUIDE FOR MAKING POST-REGISTRATION CHANGES, INCLUSIONS, NOTIFICATIONS AND CANCELLATIONS OF MEDICINES; when comparison of the dissolution profiles is applicable, the place of manufacture in the bioequivalence study will be used as a reference.

b) A maximum of three manufacturers of the drug will be accepted, irrespective of the number of centres manufacturing the medicine.

c) The process for applying for registration of national and imported generic medicines must consist entirely of the documentation described below:

1. Original copy of the proof of payment of the health surveillance inspection charge, or proof of exemption, as the case may be.

2. Copy of the updated company Operating Licence (Health Permit) of the manufacturer(s) or producer(s) of the medicine.

3. Copy of the company's Operating Authorisation or, when applicable, of the Special Operating Authorisation, published in the DOU.

4. Copy of the updated Certificate of Good Manufacturing and Control Practice (CGMCP) issued by Anvisa for the line of production in which the medicine to be registered will be manufactured.

5. For imported medicines:

5.1. Present the medicine Registration Certificate, issued by the local health authority, stating the place of manufacture or production of the medicine to be registered in Brazil;

5.2. Specify the state in which the medicine is to be imported, that is, as a finished product, bulk product or in the primary packaging;

5.3. Present a copy of the updated Certificate of Good Manufacturing and Control Practice (CGMCP) issued by Anvisa for the line of production in which the medicine to be registered will be manufactured;

5.4. Present a copy of the updated Certificate of Good Manufacturing and Control Practice (CGMCP) issued by Anvisa for the line of production of the manufacturing company, when the product is imported in bulk or in its primary packaging;

5.5. Present the specifications and methodology used by the importer in the quality control, which must be the same as those presented by the manufacturer of the medicine.

6. Copy of the protocol of the Notification of Pilot-Batch Production with the protocol number supplied by Anvisa, if there is one.

7. Copy of the updated Certificate of Technical Responsibility of the company holding the registration, issued by the Regional Pharmacy Council of the federal unit in which the pharmaceutical company is operating.

8.

9. compliance with the conditions established in current legislation on the control of Transmissible Spongiform Encephalopathy (TSE).

10. application forms - FP-1 and FP-2 – duly completed.

10. Format of the instructions and layout of the primary and secondary packaging of the medicine, in accordance with specific legislation.

10.1. The information contained in the instructions for the generic medicine must not be less than that contained in the instructions for the reference medicine, and Anvisa reserves the right to request additional information if there is a technical recommendation to do so. A copy of the instructions for the reference medicine presently being sold must be attached to the application.
10.2. With regard to the packaging of medicines produced by official pharmaceutical laboratories, this must conform to specific regulations.

11. Liquid multiple-dose and semi-solid pharmaceutical forms for intravaginal use must be accompanied by their respective dose applicators, in a suitable quantity for administration of the medicine.

12. Production report
12.1. Standard form; production process; equipment used in the manufacture of the medicine with details of the design, the working principle and the individual maximum capacity; and a statement of the industrial batch size;
12.2. Full description of the master formula with the names of the components, preserving the denomination used in the BCD, CID or the denomination described in the Chemical Abstract Substance (CAS), in that order of precedence;
12.3. Description of the quantity of each substance, expressed in decimal metric system or standard units, with a statement of its function in the formula and the respective quality specification reference described in *Farmacopéia Brasileira*, or, failing this, in some other official compendium authorised by ANVISA;
12.4. Copy of complete production and quality control dossiers, including the production order, the detailed production process and process control, relating to the three pilot-batches manufactured, for which the Production Notification was submitted previously when applying for registration. For national medicines already registered in the Country and imported medicines, the production dossier must relate to three industrial batches manufactured during the last three years. In the case of medicines in three or more different concentrations and proportional formulations, the dossiers for the lowest and highest concentrations must be submitted.
12.5. Additional documentation when more than one manufacturer of the medicines is being submitted.

a) This documentation refers to batches of the medicines which were not submitted to pharmaceutical equivalence and bioequivalence studies, when more than one manufacturer of the drugs is being submitted;

b) This documentation does not include the three batches whose production and quality control dossiers were used for the pharmaceutical equivalence, bioequivalence and stability studies.

12.5.1. Production and quality control dossier of a batch of the medicine produced with the drug, relating to each manufacturer submitted;
12.5.2. Results and evaluation of the accelerated stability study of one batch of the medicine produced with the drug, relating to each manufacturer submitted, in accordance with the GUIDE FOR CARRYING OUT STABILITY STUDIES;
12.5.3. For solid pharmaceutical forms, submit the comparative dissolution profile with the medicine which was submitted to the bioequivalence and pharmaceutical equivalence studies, in accordance with the GUIDE FOR CARRYING OUT THE STUDY AND PREPARATION OF THE REPORT ON THE PHARMACEUTICAL EQUIVALENCE AND DISSOLUTION PROFILE. When there is more than one concentration of the medicine, the profiles of all the concentrations must be compared, using as a reference the medicine which was subjected to the bioequivalence and pharmaceutical equivalence studies.
12.5.4.

13. Quality control report on the raw materials
13.1. Excipients
13.1.1. State the bibliographical reference (official compendium) recognised by ANVISA of all the excipients used in formulating the medicine. In the case of an excipient which is not described in the official compendiums recognised by ANVISA, submit the specifications and the analysis methods used.

13.2. Drug(s)

a) The company applying for registration must send copies of the original documents listed below of the company(ies) manufacturing the drug(s); a maximum of three manufacturing companies may be accepted;

b) The drug documentation must be submitted on the producing company's letterhead.

13.2.1. General details of the manufacturing company with the full address of the place where the medicine is manufactured;
13.2.2. Synthesis route, describing the intermediary molecules, their chemical names and solvents used;
13.2.3. Description of the manufacturer's specifications;
13.2.4. Identification and analytical methods used by the manufacturer;
13.2.5. Quantification and limits of the main contaminants, according to the medicine's synthesis route;
13.2.6. Details of the contents of the stereoisomers, in the case of drugs which may feature quirality, where the proportion of stereoisomers could compromise the efficacy and safety of the medicine;
13.2.7. Information and determination of the probable polymorphs and the analytical methodology for medicines featuring polymorphism;
13.2.8. Validation of the analytical methods employed, when they do not follow pharmacopeic methodology;
13.2.9. Copy of the quality control analytical report supplied by the manufacturer of the drug;
13.2.10. Specify the manufacturer of the drug(s) used in producing the medicine which is subjected to the pharmaceutical equivalence and bioequivalence study, when applicable;
13.2.11. The manufacturer(s) of the drug(s) are allowed to send the documentation specified in this item directly to Anvisa, and the documentation must be duly identified with the process number it relates to.

14. Quality control report on the medicine
14.1. Analytical methods and specifications, and submission also of these documents on a diskette or CD-ROM;
14.2. Validation of the analytical methods employed, in accordance with the GUIDE TO VALIDATING ANALYTICAL AND BIOANALYTICAL METHODS.

15. Stability studies
15.1. Results and evaluation of the accelerated stability study and the long-duration stability study of the three batches, in accordance with the rules in the GUIDE FOR CARRYING OUT STABILITY STUDIES;
15.2. For generic medicines imported in bulk, submit the results and the evaluation of the studies of accelerated and long-duration stability in their primary packaging, in accordance with the GUIDE FOR CARRYING OUT STABILITY STUDIES;
15.3. For national medicines already registered in the Country and imported medicines, also for medicines whose expiry date exceeds 24 months, submit the results and evaluation of the completed long-duration stability study, having regard to the established expiry date;
15.4. In the case of medicines with three or more different concentrations and proportional formulations, submit the results and evaluation of the stability study of the lowest and highest concentrations.

16. Data on the primary packaging and dosing applicators
16.1. Analytical methods and specifications used in the quality control of the primary packaging, and in the quality control of the dosing applicators, if any.

17. Pharmaceutical equivalence report

a) Medicines which are presented in the form of a coated tablet whose reference medicine is an uncoated tablet, or vice versa, may be registered as a generic medicine provided that the coating does not have any gastro-protective function.

17.1. Pharmaceutical equivalence technical report/certificate produced with the reference medicine sold in the Country, in accordance with the GUIDE FOR CARRYING OUT THE STUDY AND PREPARATION OF THE REPORT ON THE PHARMACEUTICAL EQUIVALENCE AND DISSOLUTION PROFILE.

18. Biopharmacotechnical tests report

a) The types of medicines exempt from the bioequivalence study and the cases in which this study may be replaced by a pharmaceutical equivalence test are defined in the GUIDE TO THE EXEMPTION FROM AND REPLACEMENT OF BIOEQUIVALENCE STUDIES;

b) In cases where the exemption is based on a comparison of the dissolution profiles, this must be carried out in laboratories duly authorised by ANVISA using the same analytical methodology as that employed in the pharmaceutical equivalence. In the case of a non-pharmacopeic method, the comparative dissolution profiles must be established using the test and reference medicines under various conditions, which must include at least three different means of dissolution in accordance with the GUIDE FOR CARRYING OUT THE STUDY AND PREPARATION OF THE REPORT ON THE PHARMACEUTICAL EQUIVALENCE AND DISSOLUTION PROFILE;

c) Immediate release oral formulations using active principle(s) which have high solubility, high intestinal permeability and a wide therapeutic window, will be exempt from the bioequivalence studies, provided that they have been exempted from proof of relative bioavailability by the regulatory bodies of the United States (FDA) and Europe (EMEA), and documents are submitted to prove this exemption

d) The bioequivalence study must be carried out using the same batch as that used in the pharmaceutical equivalence study;

e) The bioequivalence study must be carried out in accordance with the GUIDE TO THE TESTING OF THE RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE OF MEDICINES, using the reference medicine indicated by ANVISA and sold in the country;

f) Bioequivalence studies whose design is not suited to statistical treatment will not be accepted, even if the acceptance criteria are in accordance with the recommendations.

18.1. Technical bioequivalence study report, prepared in accordance with the GUIDE TO PREPARING THE TECHNICAL RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE STUDY REPORT. ANVISA may require complementary studies if it considers them necessary.

18.1.1. The company must attach to the report:

18.1.1.1. Copy of the FP1 and FP2;

18.1.1.2. Copy of the cover sheet (format in Appendix II to these Regulations);

18.1.1.3. Complete description of the formulation used in the bioequivalence study, stating the quantities and functions of each substance;

18.1.1.4. Pharmaceutical equivalence technical report/certificate in accordance with the GUIDE FOR CARRYING OUT THE STUDY AND PREPARATION OF THE REPORT ON THE PHARMACEUTICAL EQUIVALENCE AND DISSOLUTION PROFILE, of the products used in the bioequivalence study;

18.1.1.5. Where exemption from bioequivalence is requested, submit a comparative dissolution study report (dissolution profiles) in accordance with the GUIDE FOR CARRYING OUT THE STUDY AND PREPARATION OF THE REPORT ON THE PHARMACEUTICAL EQUIVALENCE AND DISSOLUTION PROFILE;

18.1.1.6. Copy of the Certificate of Good Medicines Bioavailability and Bioequivalence Practice of the centre(s) carrying out the study, which must be valid for the period during which the study is carried out.

IV – Medicines which will not be accepted as generic.

a) The following will not be admitted for the purpose of registration of a generic medicine:

1. Medicines which are exempt from registration in accordance with RDC Resolution No. 123 of 29 May 2003.

2. Single small volume parenteral solutions (SVPS) and large volume parenteral solutions (LVPS), containing no drug, such as injectable water, glucose solutions, sodium chloride, other electrolytic compounds or sugars.

3. Biological and immunotherapeutic products derived from plasma and human blood.

4. Products obtained by biotechnology, excluding antibiotics, fungicides and others, at Anvisa's discretion.

5. Phytotherapeutic products.

6. Medicines containing vitamins and/or mineral salts.

7. Antiseptics for hospital use.

8. Products for diagnostic purposes and radiological contrast.

9. Medicines exempt from medical prescription, contained in the LIST OF SPECIFIC THERAPEUTIC GROUPS AND INDICATIONS (STGI), except:

9.1. Antacids, antiemitics, eupeptics, antiphysetics, antiflatulents and carminatives;
9.2. Non-narcotic analgesics;
9.3. The anti-inflammatories naproxen, ibuprofen and ketoprofen and all the topical non-steroidal anti-inflammatories;
9.4. Expectorants, balsamics, mucolytics, cough sedatives;
9.5. Topical antifungicides and antimycotics;
9.6. Muscular relaxants;
9.7. The oral antiparasitics, antihelmintics, mebendazol and levamizol and all the topical antiparasitics, scabicides, ectoparasiticides;
9.8. Antihistamines;
9.9. Antispasmodics;
9.10. The topical antibactericides bacitracine and neomicine;
9.11. Antiphlebitics;
9.12. Topical antihaemorrhoid treatments;
9.13. Anti-tobacco treatments;
9.14. Topical nasal decongestants and the systemic nasal decongestant phenylephrine;

V – Post-registration measures

1. After publication of the registration, the generic medicine manufacturer must supply Anvisa with:

1.1. Proof of distribution of the first three batches manufactured, to allow Anvisa, if it wishes, to collect samples for control analysis;
1.2. Results and final evaluation of the long-duration stability study of the first three batches produced, in accordance with the timetable approved by Anvisa. In the case of registered medicines, whose stability study does not conform to the description in the GUIDE TO THE CARRYING OUT OF STABILITY STUDIES, a fresh study must be presented;
1.3. Report on the incidence of adverse reactions and therapeutic inefficacy;
1.4. The company must produce evidence of the start of sales of this medicine, by submitting a copy of three bills of sale to Anvisa, preferably within 1 year of the date of publication of registration of the generic medicine in the DOU, in order to update the list of generic medicines sold, which must be available at pharmacies and drug stores, in accordance with specific legislation;
1.4.1. Official laboratories are exempted from presentation of the bills of sale, but they must produce evidence of production and distribution of the medicines.

2. Post-registration changes, inclusions, notifications and cancellations.

a) Anvisa must be sent all the documentation concerning the description of the changes, inclusions, notifications and cancellations to the medicine produced, after registration was granted,

as instructed in the GUIDE TO THE MAKING OF POST-REGISTRATION CHANGES, INCLUSIONS, NOTIFICATIONS AND CANCELLATIONS OF MEDICINES;

b) The company may only sell the product with the proposed change and/or inclusion after publication of acceptance of the request in the DOU;

c) Several changes and/or inclusions for the same medicine can be requested, provided that the relevant documentation is presented for each of them;

d) If it is observed that there has been an inclusion or change to a medicine which had not previously been notified to Anvisa and approved by it, the company will be penalised by cancellation of the medicine registration.

3. Criteria and conditions for renewal of the registration

a) In order to renew the registration of a generic medicine, the company must submit the following documentation:

3.1. Application forms (FP-1 and FP-2), duly completed;
3.2. Original copy of the proof of payment of the health surveillance inspection charge, or exemption from it, as the case may be;

3.3. Copy of the updated Certificate of Good Manufacturing and Control Practice (CGMCP) issued by Anvisa for the line of production in which the medicine whose registration is to be renewed, is manufactured;
3.4. Copy of the updated Certificate of Technical Responsibility of the company holding the registration, issued by the Regional Pharmacy Council of the federal unit in which the pharmaceutical company is operating.
3.5. Copy of bills of sale to prove the medicine is being sold. Present a declaration of commercial products not being sold for which the company may be interested in maintaining the registration;
3.5.1. In the case of Official Laboratories, if there has been no production of the medicine during the said period, supply an explanation of why it is not being sold.
3.6. Copy of the latest version of the instructions accompanying the product on its commercial packaging. Supply a copy of the instructions for the reference medicine presently being sold, if it is intended to alter and/or update the instructions which were sent when the medicine was registered;
3.7. Layout of the primary and secondary packaging of the medicine;
3.8. List of all the post-registration changes and/or inclusions which have taken place during the last product registration validity period, together with a copy of the publication in the DOU, or failing this, a copy of the protocol of the application(s) concerned;
3.9. For imported medicines:
3.9.1. Copy of the updated Certificate of Good Manufacturing and Control Practice issued by ANVISA for the manufacturing company's line of production, where import of the product in bulk or in its primary packaging is involved;
3.9.2. Copy of the reports of the physical-chemical, chemical, microbiological and biological quality control done by the importer in Brazil.
3.10. Results and evaluation of the long-duration stability study, in accordance with the rules in the GUIDE FOR CARRYING OUT STABILITY STUDIES;
3.11. Bioequivalence study carried out with the reference medicine sold in the Country, in accordance with the rules of the GUIDE TO THE TESTING OF THE RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE OF MEDICINES, if the registration was granted on the basis of a bioequivalence study done with a reference medicine not sold in the country.

4. Situations in which a new study may be required to check the bioequivalence

a) Anvisa may require a new study to determine the bioequivalence of a generic medicine in the following situations:

4.1. When there is clinical evidence that the generic medicine does not offer therapeutic equivalence in relation to the reference medicine;
4.2. When there is documentary evidence that the generic medicine is not bioequivalent in relation to the reference medicine;
4.3. When there is a risk of damage to health;

4.4. When there are changes and inclusions in the medicine which would justify a new check on interchangeability.

VI – Criteria for prescribing and dispensing generic medicines

1. Prescription
1.1. Within the scope of the Single Health System (SUS), prescriptions by the licensed practitioner concerned must adopt the Common Brazilian Denomination (CBD), or failing this, the Common International Denomination (CID);
1.2. In private health services, the prescription will be at the discretion of the practitioner concerned, and may be according to the Common Brazilian Denomination (CBD), or failing this, the Common International Denomination (CID), or using a commercial name;
1.3. If the licensed prescriber decides that the prescription should not be interchangeable, this must be stated for each item prescribed, clearly, legibly and unambiguously in handwriting by the prescriber, and no other forms of inscription will be permitted.

2. Dispensing
2.1. The licensed pharmacist may replace the prescribed medicine by the corresponding generic medicine, subject to any express restrictions by the licensed subscriber;
2.2. In such cases, the licensed pharmacist must note the replacement in the prescription, rubber stamp it with his/her name and registration number with the Regional Pharmacy Council, and date and sign it;
2.3. In the case of prescriptions using the Common Brazilian Denomination (CBD) or the Common

International Denomination (CID), dispensing of the reference medicine or the corresponding generic medicine only will be permitted;

2.4. It is the duty of the licensed pharmacist to explain in detail the product dispensed to the patient or user, and to supply all necessary guidance on the proper use of the generic medicine;

2.5. Replacement by the generic medicine must conform to the guidelines in the list of generic medicines registered by Anvisa;

2.6. The list of generic medicines must be announced by Anvisa via the media.

APPENDIX II

COVER SHEET OF THE PROCESS OF REGISTRATION AND POST-REGISTRATION OF GENERIC MEDICINES

Submission	Post-Registration (state the application)
Compliance with Requirements	Amendment

Details of the applicant company
Applicant company
Telephone
Fax
E-mail
Technical Manager
Date of publication of the CGMCP in the DOU
Do you have an outsourcing contract approved by Anvisa?

Details of the generic medicine process
Country of origin of the medicine
Pharmaceutical form
Concentration
Therapeutic class
Name of the laboratory carrying out the

bioequivalence study
Country in which the bioequivalence study was carried out

Name and full address of the manufacturer of the
drug used in the medicine, with which the
pharmaceutical equivalence and
bioequivalence/relative bioavailability study was carried out
Batch number and date of manufacturer of the medicine

with which the pharmaceutical equivalence study was carried out

Batch number and date of manufacturer of the medicine

with which the bioequivalence/relative bioavailability study was carried out

Details of the reference medicine company
reference medicine
Laboratory which manufactured the
reference medicine