Brazilian Sanitary Surveillance Agency

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Draft Resolution no. 52 of 1 September 2006
Brazilian Official Journal of 04/09/2006

The Collegiate Board of Directors of the Brazilian Sanitary Surveillance Agency (ANVISA), exercising the powers conferred upon it by art. 13 point IV of the Regulation approved by Decree no. 3029 of 16 April 1999, and in view of the provisions of art. 16 point V, art. 11 point IV and art. 35 of the ANVISA Regulation approved by Decree no. 3029 of 16 April 1999, and in view of the provisions of art. 54 point V and §1 of the Internal Regulations approved pursuant to Appendix I of ANVISA Administrative Act no. 354 of 11 August 2006, republished in the Brazilian Official Journal of 21 August 2006,

Adopts ad referendum the following Draft Resolution and orders its publication:

Art. 1 The 30 (thirty) day period during which criticisms and suggestions relating to the appended proposed "TECHNICAL REGULATIONS FOR THE REGISTRATION OF INDUSTRIALISED DYNAMISED DRUGS" can be submitted starts as of the date of publication of this Draft Resolution.

Art. 2 The proposed Technical Regulations will be available, in full, throughout the consultation period at the electronic address www.anvisa.gov.br and suggestions must be sent in writing to the following address: Agênica Nacional de Vigilância Sanitária, SEPN 515, Bloco “B” Ed. OMEGA, Asa Norte, Brasília, DF, CEP 70.750.541 or email: gmefh@anvisa.gov.br.

Art. 3 At the end of the period specified in art. 1, the Brazilian Sanitary Surveillance Agency will liaise with the Bodies and Entities involved and those that have expressed an interest in the subject, so that they can appoint representatives in the subsequent discussions with a view to the consolidation of the final text.

DIRCEU RAPOSO DE MELLO

APPENDIX

Resolution of the Collegiate Board of Directors (RDC) no. ……. of ……. 2006

Provisions on the registration of industrialised dynamised drugs

The Board of Directors of the Brazilian Sanitary Surveillance Agency, exercising the powers conferred upon it by art. 11 point IV of the ANVISA Regulation approved by Decree no. 3029 of 16 April 1999, together with art. 111 point 1, paragraph “b”, § 1 of the Internal Regulations approved by Administrative Act no. 593 of 25 August 2000, republished on 22 December 2000, at a meeting held on 6 March 2003,

considering the need to implement action contributing to the improvement of the quality of health care;

considering that the Brazilian Sanitary Surveillance Agency is responsible for setting out guidelines for the production sector, in accordance with the provisions of Law no. 6360 of 23 September 1976, Decree no. 57477 of 28 December 1965 and these Regulations;

considering that art. 41 of Law no. 9782 of 26 January 1999 confers on ANVISA powers for the debureaucratisation and speeding up of drug registration procedures, and also permits measures for exemption from registration of drugs;

considering that the drugs classified as exempt from registration, despite not being given a registration number, are in fact notified for the purposes of records for the monitoring of the market and quality control;

considering the provisions of article 61 of Secretary for Sanitary Surveillance/Ministry of Health Administrative Act no. 344 of 12 May 1998 and its updates;

considering the definitions set out in the GLOSSARY OF LEGAL DEFINITIONS available on the ANVISA web site;

considering the definition of drug given in Art. 4 point II of Law 5991 of 1973, which implies a therapeutic action;

considering arts. 33 and 34 of Decree no. 79094 of 5 January 1977, which permits the registration of industrialised homeopathic drugs with proven therapeutic action;

considering Decree 57477 of 1965, which contains provisions on the handling, pharmacopoeia, industrialisation and sale of products used in homeopathy and gives other provisions;

considering Decree-Law no. 78841 of 1976, which approves the first edition of the Farmacopéia Homeopática Brasileira [Brazilian Homeopathic Pharmacopoeia];

considering Administrative Act no. 1180 of 1997, which approves Part 1 of the Second Edition of the Farmacopéia Homeopática Brasileira, which, as of the publication of the Administrative Act, comes into force and the use of which becomes obligatory throughout Brazil;

considering the Resolution of the Brazilian Health Council of 15/12/05, which approves the National Policy for Integrative and Complementary Practices in the Single Health System, Administrative Act no. 971 of 3 May 2006, which approves the National Policy for Integrative and Complementary Practices (PNPIC) in the Single Health System and Administrative Act no. 1600 of 17 July 2006, which approves the creation of the Observatory of Anthroposophic Medicine Trials in the Single Health System;

considering CFM Resolution no. 1000 of 1980, which recognises, in Brazil, Homeopathy as a medical speciality, CFMV Resolution no. 625 of 1995, which recognises Veterinary Homeopathy as a veterinary medical speciality, CFF Resolution no. 335 of 1998, which recognises Homeopathic Pharmacy and homeopathic pharmacists as a speciality in the training of pharmaceutical professionals, together with the existence of a specific pharmacopoeia, in accordance with Administrative Act no. 1180 of 1997, and CFM Resolution no. 23 of 1993, which recognises Anthroposophic Medicine as a medical practice;

considering paragraph 269 of the Organon of the Medical Art, 6th edition, Samuel Hahnemann, which recognises the existence of dynamised drugs;

considering the low health risk, with regard to toxicity, of industrialised dynamised drugs;

considering the different therapeutic applications of dynamised drugs, such as homeopathy, homotoxicology and anthroposophic medicine;

considering that the Farmacopéia Homeopática Brasileira and the Manual de Normas Técnicas para Farmácias Homeopáticas [Manual of Technical Standards for Homeopathic Pharmacies],

current editions, recognise the existence of “homeopathic formulations” with two or more liquid or solid active ingredients;

considering that the Brazilian, German (GHP/HAB), American (HPUS), British (BHP), Mexican and Indian Homeopathic Pharmacopoeias, as well as the European (Ph. EUR) and French (PhFr) Pharmacopoeias, Homeopathie-Pharmacotechnie et Monographies des Medicaments Courants [Homeopathy-Pharmaceutical Technology and Monographs of Common Drugs] Volumes I and II, and the Anthroposophic Pharmaceutical Codex (APC) consider methods of production and analysis relevant to all applications of dynamised drugs;

considering that the Brazilian, German, American, British, European, French, Japanese and Mexican Pharmacopoeias are compendia recognised by ANVISA and consider methods of analysis relevant to dynamised drugs with regard to pharmaceutical forms and inactive ingredients;

considering the Anthroposophic Pharmaceutical Codex (APC) published by the International Association of Anthroposophic Pharmacists (IAAP);

considering that the Homeopathic Pharmacopoeia of the United States of America (HPUS) publishes a table of safe potencies for the dispensation of dynamised drugs, in which the limits of the potencies of the drugs for dispensation on prescription or for free dispensation, based on acute toxicity data, are determined;

Adopts the following Resolution and I, the Chairman, order its publication.

Art. 1 This Resolution deals with the registration and notification of marketing of industrialised dynamised drugs.

§1 The homeopathic, anthroposophic and antihomotoxic drugs covered in the definitions in Art. 2 of these regulations are considered to be dynamised drugs.

§2 The provisions of these regulations do not prejudice the application of stricter provisions to which narcotic, psychotropic and precursor substances or any other product subject to special controls are subject.

§3 All pharmaceutical forms (globules, tablets, powders, ovules, suppositories, creams, pomades, gels, oral solutions, injectable solutions, opthalmic solutions, nasal solutions and other pharmaceutical forms) for internal and/or external use are subject to registration and notification, in accordance with the limitations set out in these regulations.

Art. 2 The following definitions apply for the purposes of the provisions of this Resolution:
Dynamised drugs: are prepared from substances that undergo dilution, trituration procedures or rhythmic agitation with a preventative or curative aim, to be administered in accordance with homeopathic, homotoxicological and anthroposophic therapeutics.

Single-component homeopathic drugs: dynamised drugs prepared from a single active ingredient, in any potency, according to preparation and control methods described in the current edition of the Farmacopéia Homeopática Brasileira and other homeopathic pharmacopoeias or official compendia recognised by ANVISA, with proven therapeutic action described in the homeopathic materia medica or the official homeopathic compendia recognised by ANVISA, clinical studies or scientific journals. These drugs must be notified or registered.

Compound homeopathic drugs: dynamised drugs prepared from two or more active ingredients, in any potency, based on the principles of homeopathy, the methods of preparation and control of which are described in the current edition of the Farmacopéia Homeopática Brasileira and other homeopathic pharmacopoeias or official compendia recognised by ANVISA,

with proven therapeutic action described in the homeopathic materia medica or the official homeopathic compendia recognised by ANVISA, clinical studies or scientific journals. These drugs must be registered.

Single-component anthroposophic drugs: dynamised drugs prepared from a single active ingredient, in any potency, based on the principles of anthroposophy, the methods of preparation and control of which are described in the Homeopathic Pharmacopoeias or the Anthroposophic Pharmaceutical Code or official compendia recognised by ANVISA, with proven therapeutic action described in the homeopathic materia medica or official anthroposophic compendia recognised by ANVISA, clinical studies or scientific journals. These drugs must be notified or registered.

Compound anthroposophic drugs: dynamised drugs prepared from two or more active ingredients, in any potency, from mother tinctures, or prepared from a single active ingredient in more than one potency, based on the principles of anthroposophy, the methods of preparation and control of which are described in the Homeopathic Pharmacopoeias and the Anthroposophic Pharmaceutical Codex or official compendia recognised by ANVISA, with proven therapeutic action described in the homeopathic materia medica or official anthroposophic compendia recognised by ANVISA, clinical studies or scientific journals. These drugs must be registered.

Antihomotoxic drugs: are dynamised drugs prepared from one or more active ingredients, in any potency, or in more than one potency (in potency accord) of the same substances, based on the principles of homeopathy and homotoxicology, the preparation and control methods of which must compulsorily follow the official methods described in the current edition of the German Homeopathic Pharmacopoeia, or other homeopathic pharmacopoeias and official compendia recognised by ANVISA, and the formula of which is made of substances with proven therapeutic action, described in the homeopathic and antihomotoxic materia medica recognised by ANVISA, clinical studies or scientific journals. These drugs must be notified or registered.

Dynamisation: process of dilution followed by succussion and/or successive triturations of the active ingredient, into an appropriate inert ingredient, the aim of which is to enhance the medicinal power.

Dilution: reduction of the concentration of the active ingredient or starting point for the addition of an appropriate inert ingredient.

Active ingredient: medicine, drug or derived pharmaceutical form used for the preparation of the drug.

Potency: quantitative indication of the number of successive stages of dynamisation to which the active principles of the formula have been subjected. Refers to the medicinal strength of the active ingredient enhanced through dynamisation.

Mother tincture (MT): pharmaceutical preparation, in solution form, resulting from the dissolving and/or extractive action of an inert ingredient on a given active ingredient, in accordance with pharmaceutical technology described in the compendia recognised by ANVISA, from which the dynamised drugs are obtained.

Trituration (TRIT): basic (for solid or insoluble active principles) or intermediate pharmaceutical preparation, resulting from the mechanical action of an appropriate excipient on (a) given active principle(s), in accordance with pharmaceutical technology described in the compendia recognised by ANVISA, from which the dynamised drugs are obtained.

Art. 3 For the purposes of defining the different classes of dynamised drugs, it is considered that:

§1 Single-component or compound homeopathic drugs must comply with homeopathic pharmaceutical technology and have a therapeutic indication validated by the information contained in the homeopathic materia medica, toxicological data, scientific articles and/or clinical studies, in accordance with the principle of similitude.

§2 Dynamised drugs the therapeutic indications of which are defined in accordance with the concepts of anthroposophic or homotoxic medicine, even if they are prepared in accordance with homeopathic pharmaceutical technology, will be classified as anthroposophic or antihomotoxic respectively.

§3 Dynamised drugs prepared in accordance with anthroposophic pharmaceutical technology and/or the therapeutic indication of which is based on the concepts of anthroposophic medicine will be classified as anthroposophic drugs.

§4 Drugs prepared in accordance with anthroposophic pharmaceutical technology will be classified as anthroposophic, even if their therapeutic indications are based on homeopathic materia medica.

Art. 4 Dynamised drugs subject to notification must proceed as set out in Appendix I of this Resolution, and the notification must be renewed at the time of renewal of the GMPQC certificate or whenever the information given in the notification is amended.

Art. 5 Dynamised drugs subject to registration must have a therapeutic indication and meet the requirements set out in Appendix II of this Resolution, and the registration must be renewed every five years.

Art. 6 The criteria for the compulsory need for a prescription in the dispensation of dynamised drugs will comply with the Table of Potencies for the Registration and Notification of Dynamised Drugs, in accordance with a specific Resolution.

§1 pharmaceutical forms for external use will be exempt from the obligatory use of a YELLOW BORDER on their packaging and labelling.

§2 it is obligatory that injectable pharmaceutical forms be dispensed on prescription.

§3 for substances that do not appear in the Table of Potencies for the Registration and Notification of Dynamised Drugs, the manufacturer is responsible for proving that such substances are safe to use in the intended concentration, through clinical, non-clinical or toxicological studies or scientific bibliographies appropriate to the profile of the substance. The proof submitted will be assessed by a Committee formed by ANVISA to this end.

§4 compound industrialised dynamised drugs the formulation of which contains one or more components the potency of which implies the need for prescription will compulsorily have a yellow border on their packaging and labelling, with the words "*Sold on prescription"*.

Art. 7 The wording on the packaging must comply with the regulations for the labelling of drugs.

Single paragraph: point 8 of Appendix I of RDC 333/03 henceforth has the following wording:

8. Industrialised Dynamised Drugs
8.1 The labelling of industrialised dynamised drugs must contain the name of the active ingredient(s) using the official nomenclature of the pharmacopoeias officially recognised by ANVISA or a confirmed synonym, the scale, potency, route of administration and pharmaceutical form.
8.1.1 All packaging must also contain the scale, dynamisation, preparation method, route of administration and pharmaceutical form.

8.2 Industrialised homeopathic drugs exempt from registration (subject to notification) contained in the Farmacopéia Homeopática Brasileira must show on all packaging the words “FARMACOPEIA HOMEOPATICA BRASILEIRA” in 1.5 mm upper case lettering, and must contain the relevant scale and potency, the route of administration and the pharmaceutical form.
8.2.1 For industrialised dynamic drugs exempt from registration (subject to notification) not entered in the Farmacopéia Homeopática Brasileira, but entered in other pharmacopoeias or compendia recognised by ANVISA, the word "HOMEOPATHIC" or "ANTHROPOSOPHIC" OR "ANTIHOMOTOXIC" must be included as applicable.
8.3 Industrialised dynamised drugs exempt from registration (subject to notification) cannot show any therapeutic indication on their labelling.
8.4 The labelling of industrialised dynamised drugs exempt from registration (subject to notification) must contain the following phrase: “*Do not use this drug without guidance from your doctor*” in 1.5 mm upper case lettering.
8.5 All packaging for industrialised dynamised drugs subject to registration must contain the text “HOMEOPATHIC” or “ANTHROPOSOPHIC” or “ANTIHOMOTOXIC” in accordance with the therapeutic applicability proved on registration of the industrialised dynamised drug, in upper case lettering 30% of the size of the brand name of the product.

Art. 8 The leaflet for industrialised dynamised drugs subject to registration will comply with the requirements contained in Appendix IV of this Resolution. Dynamised drugs subject to notification of marketing must use the CONSUMER INFORMATION PAMPHLET instead of the leaflet, in accordance with the aforementioned Appendix.

Art. 9 The following will not be registered as dynamised drugs: combinations of synthetic, semi-synthetic, biological or phytotherapeutic drugs, vitamins/mineral salts/amino acids, or opotherapeutic drugs with dynamised active ingredient(s) in a single formulation or in two or more presentations in the same packaging for concomitant or sequential use.

§1 the addition of colorants, sweeteners, flavones, flavourings or any other additive (active or inert) will not be permitted in homeopathic drug formulations.

§2 the combination in a single formulation of active principles that have specific pharmacological incompatibilities with each other is prohibited, on the assumption that they will have antagonistic therapeutic actions.

§3 only anthroposophic drugs can contain mother tinctures without their composition.

Art. 10 Only decimal and centesimal scales are permitted within the scope of this Resolution, and conversion between scales is prohibited.

Art. 11 On the first renewal after the publication of this Resolution, the holders of registrations or records or notifications of dynamised drugs must comply with this Resolution, with the exception of the presentation of a copy of the memorandum of notification of production of pilot batches.

§1 At the company’s discretion, compliance with this Resolution may be required before the renewal period. Such requests must be sent to ANVISA in the form of an official letter, accompanying justification and all relevant documents, together with the notifications necessary.

§2 Products that are in the process of being revalidated or registered (apart from those that already fulfil the requirements and/or have a period to fulfil the requirements that ends on the publication of this Resolution) must be brought into compliance through supplements to the process. The supplements must be sent by the company within 90 (ninety) days of the publication of this Resolution, regardless of the expiry of the period for the fulfilment of the requirements set out.

§3 If ANVISA deems it necessary, it may request from the company the classification of the product(s) with analysis of the fulfilment of requirements underway on the publication of this Resolution. In this case, the company will have a non-extendable period of 90 (ninety) days from the time of ANVISA's request to comply.

§4 The publication of this Resolution will not alter the periods for the fulfilment of requirements already set out by ANVISA.

§5 If there is any change in the product category (from "homeopathic" to "anthroposophic" or "antihomotoxic"), the company will have 180 days (from the issuing of a favourable opinion by ANVISA) to bring the packaging and leaflet (or pamphlet, as applicable) for the drug into compliance. The final layouts must be sent to ANVISA in the form of notification at the end of this period.

Art. 12 ANVISA may, at any time and at its discretion, require additional proof relating to the identity and quality of the components, and to the safety and efficacy of the drug, if there is any doubt or supervening event that gives rise to additional assessments, even after the granting of registration or notification.

Art. 13 ANVISA will set out provisions in Specific Resolutions on the following:

§1 Guide for the performance of dynamised drug stability studies;

§2 List of bibliographic references officially accepted by ANVISA within the scope of this Resolution;

§3 Table of Potencies for the Registration and Notification of Industrialised Dynamised Drugs;

Art. 14 Cases not provided for in this resolution will be assessed as appropriate by ANVISA.

Art. 15 This Resolution will come into effect on the date on which it is published, and revokes RDC 139 of 2003 and arts. 12, 16, 18, 19 and 20 of Administrative Act no. 17 of 22 August 1966.

Appendix I – NOTIFICATION OF MARKETING OF DYNAMISED DRUGS

Appendix II – PROCEDURES FOR THE REGISTRATION AND RENEWAL OF REGISTRATION OF DYNAMISED DRUGS

Appendix III – POST-REGISTRATION PROCEDURES FOR DYNAMISED DRUGS

Appendix IV – CONSUMER INFORMATION LEAFLET and PAMPHLET for DYNAMISED DRUGS

Appendix I
NOTIFICATION OF MARKETING OF INDUSTRIALISED DYNAMISED DRUGS

Measures prior to notification:
Notify the production of pilot batches, in accordance with the current Guide for the Notification of Pilot Batches of Drugs (except for imported products).

Notification measures:
1. The notification of marketing of industrialised dynamised drugs is initiated by an electronic procedure available on the ANVISA web site.
1.1 Only single-component dynamised drugs exempt from prescription, as set out in the Table of Potencies for the Registration and Notification of Industrialised Dynamised Drugs, must be notified.
1.2 Notified dynamised drugs cannot mention any therapeutic indication.
1.3 Notified dynamised drugs can be dispensed in any pharmaceutical form, except injectable; one notification per pharmaceutical form is necessary.
1.4 If the company wishes to market a dynamised drug exempt from prescription with a specific therapeutic indication, it must obtain industrialised dynamised drug registration in accordance with Appendix II of these regulations.
1.5 A list of companies and notified products will be made available on the ANVISA web site immediately after notification.
2. Stability studies on the notified dynamised drugs must be carried out in accordance with the STABILITY GUIDE FOR INDUSTRIALISED DYNAMIC DRUGS.
3. Notification must be preceded by notification of the production of pilot batches in accordance with the GUIDE FOR THE NOTIFICATION OF PILOT BATCHES, except for products that have a current record or registration with ANVISA.
4. Notification must meet the following criteria:
4.1 Notification must be carried out only by the company with an operating permit to produce and/or import drugs.
4.2 The company must carry out an individual notification for each product in accordance with these regulations.
4.3 All notifications must be renewed on the renewal of the GMP certificate, by means of notification of each product.
4.3.1 The non-renewal of the GMPQC certificate implies the cancellation of the notification of the product.
4.4 When manufacturing of the product is suspended, the company must notify the exclusion from marketing of the product.
4.5 The updating of the information provided at the time of notification is obligatory. To this end, any alteration to the information given on electronic notification implies a new notification.
4.6 Notifications are exempt from the payment of a fee.
4.7 For dynamised drugs, the “concentration” field must be understood as the description of the scale and potency of the drug.
5. The labelling of notified dynamised drugs must comply with the new wording of point 8 of RDC 333/03 and the following provisions:
5.1 The labelling of the products specified in Point 1 of this Appendix must contain the following phrase: “NOTIFIED DYNAMISED DRUG – RDC No. ……../2006. AFE [operating permit] no. ……..”.
5.2 The adoption of a trade name or brand name for notified dynamised drugs is permitted.
5.3 Notified dynamised drugs must adopt the CONSUMER INFORMATION PAMPHLET FOR DYNAMISED DRUGS SUBJECT TO NOTIFICATION OF MARKETING, in accordance with Appendix IV of these regulations, instead of a leaflet.
5.4 The labelling of notified dynamised drugs must contain the following information:
5.4.1 Trade name or brand name (OPTIONAL).
5.4.2 Name of the active ingredient(s) using the official nomenclature of the pharmacopoeias and compendia recognised by ANVISA, the scale, potency, method, route of administration and pharmaceutical form.

5.4.3 Use ("adult" or "paediatric" or "adult and paediatric").
5.4.4 Contents of the packaging, expressed as volume, weight or number of pharmacotechnical units.
5.4.5 Composition: Qualitative and quantitative for the active ingredient, giving its scale and potency.
5.4.6 Inert ingredients (mention concentration in the formula).
5.4.7 The inclusion of additional information with regard to organoleptic properties is permitted.
5.4.8 Storage instructions.
5.4.9 Include the phrases: “ALL DRUGS MUST BE KEPT OUT OF REACH OF CHILDREN” and “*For the correct use of this drug, seek guidance from your pharmacist*”.
5.4.10 Include the phrase: “NOTIFIED DYNAMISED DRUG – RDC No. ……./2006. AFE no. …….”.
5.4.11 Include the highlighted phrase: “*If symptoms persist, consult your doctor.*”
5.4.12 Name of the Responsible Pharmacist and relevant CRF [Regional Pharmacy Council] number.
5.4.13 Name of the notifying company.
5.4.14 CNPJ [National Register of Judicial Persons] number of the notifying company.
5.4.15 Full address of the notifying company.
5.4.16 Manufactured by……. (where applicable).
5.4.16.1 Name of the manufacturing company.
5.4.16.2 CNPJ number of the manufacturing company.
5.4.16.3 Full address of the manufacturing company.
5.4.16.4 Telephone number of the notifying company’s Consumer Service Department.
5.4.16.5 Batch number.
5.4.16.6 Manufacturing Date.
5.4.16.7 Expiry Date
5.4.16.8 Bar code/Product Identification Number.
6. Only manufacturing companies that comply with Good Manufacturing Practice and Quality Control in accordance with current legislation and that are duly authorised/licensed by the competent Sanitary Authority can notify and manufacture dynamised drugs.
7. Drugs with a valid record or registration with ANVISA must be brought into compliance in accordance with the following provisions:
7.1 By 180 (one hundred and eighty) days after the publication of these regulations, all homeopathic drugs recorded by ANVISA as exempt from registration must comply with these regulations.
7.2 Homeopathic drugs with valid registration and that fall under these regulations can proceed with the compliance at the company's discretion or, obligatorily, on the first renewal.
8. The information given in the Notification is the responsibility of the company and will be subject to sanitary inspections by ANVISA.
9. Documents to be sent and information to be supplied at the time of electronic notification:
9.1 QUALITATIVE AND QUANTITATIVE FORMULA, including active and inert ingredients.
9.2 SCALE AND POTENCY OF THE ACTIVE INGREDIENTS
9.3 PHARMACEUTICAL FORM
9.4 TRADE NAME
9.5 STABILITY STUDY REPORT (attach file containing the report with the results, in accordance with the Guide for the stability of industrialised dynamised drugs)
9.5.1 ACCELERATED (concluded)
9.5.2 LONG-TERM (concluded or partial result of a study in progress)
9.6 LAYOUT OF THE LABELLING and CONSUMER INFORMATION PAMPHLET (attach corresponding files)
9.7 Information about the manufacturing company
9.7.1 Company name
9.7.2 CNPJ no.
9.7.3 Operating Permit
9.7.4 Good Manufacturing Practice and Quality Control Certificate (issued by ANVISA) – give the number of the Specific Resolution granting the GMPQC certificate.

9.8 Information about the notifying company
9.8.1 Company name
9.8.2 CNPJ no.
9.8.3 Operating Permit
9.8.4 Good Manufacturing Practice and Quality Control Certificate (issued by ANVISA) or satisfactory status on the Directorate General for the Inspection and Control of Ingredients, Drugs and Products (GGIMP) database available on the ANVISA web site.
10. The technical and legal documentation relating to all production sites must be sent if the company is requesting notification of a drug produced at more than one production site at the same time.

Appendix II
PROCEDURES FOR THE REGISTRATION AND RENEWAL OF REGISTRATIONS OF DYNAMISED DRUGS

Measures prior to Registration:
1. Notify the production of pilot batches in accordance with the GUIDE FOR THE NOTIFICATION OF PILOT BATCHES, except for imported products.
Registration measures:
For the purposes of registration, the company must file a single process, with separate production and quality control reports for each pharmaceutical form. All of the pages of the application must be initialled by the legal representative and technical manager of the company.
The company must have complied with all of the requirements prior to registration and submit the following documents:
1. Legal Documents:
1.1 Application forms FP1 and FP2, duly completed.
1.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU)).
1.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I.
1.4 Copy of the company's Operating Permit and Sanitary Licence.
1.5 Valid technical responsibility certificate issued by the Regional Pharmacy Council.
1.6 Good Manufacturing Practice and Quality Control (GMPQC) certificate for the production line on which the product will be manufactured; or a copy of the inspection request memorandum for the issuing of such certificate. The memorandum will be valid if the production line in question was SATISFACTORY at the last GMPQC inspection.
1.7 If the company manufacturing the product is different from the company applying for registration (including when stages of production are outsourced), the following documents for the **manufacturing company** must also be submitted:
a) Copy of the Operating Permit and Sanitary Licence.
b) Valid technical responsibility certificate issued by the Regional Pharmacy Council.
c) Good Manufacturing Practice and Quality Control (GMPQC) certificate or a copy of the inspection request memorandum for the issuing of such certificate. The memorandum will be valid if the production line in question was SATISFACTORY at the last GMPQC inspection.
d) Detailed production and quality control report.
2. Information about the production of the drug:
2.1 Pharmaceutical form.
2.2 Complete formula (name, potency, scale and method).
2.3 Detailed description of all of the stages in the production process, including the equipment used.
2.4 Brief description of the control methodology during the production process.
2.5 Minimum and maximum sizes of the industrial batches to be produced.
2.6 Description of the identification criteria for the industrial batch.
2.7 Expiry date: give the required date and provide results that prove stability in accordance with the legislation in force.

a) Give details of how the expiry date was determined and the storage of the pharmaceutical form with regard to the physical, physico-chemical and microbiological integrity of the product.
b) Give the results of the accelerated stability study, accompanied by the results of the long-term stability study (concluded or in progress).

3. Information about the quality control of the drug.

Give the following for the finished product, bulk product (if applicable), active ingredient and inert ingredient:
3.1 Analysis method and specifications.
3.2 Copy of the bibliographic reference recognised by ANVISA, in accordance with the legislation in force, in which the analysis method is described.
3.3 If the analysis method has been developed by the company, with or without the use of a bibliographic reference recognised by ANVISA, submit validation in accordance with the current GUIDE FOR THE VALIDATION OF ANALYTICAL AND BIOANALYTICAL METHODS.
3.4 Send additional information in accordance with the legislation in force on the control of Transmissible Spongiform Encephalopathy, or justification for the absence of this document, if applicable.
3.5 Labelling (primary and secondary packaging) and leaflet layouts, in accordance with the legislation in force.
3.6 Give the names of the manufacturers/suppliers of the active and inert ingredients. A maximum of three suppliers per ingredient will be permitted.
3.6.1 Attach a copy of the proof that the supplier(s) has/have SATISFACTORY status with the GGIMP, or justify the absence of this document.

4. Proof of the indication, efficacy and safety of the drug

4.1 The dynamised drug must have a therapeutic indication in accordance with the principles of homeopathy, homotoxicology or anthroposophic medicine (depending on the category into which it falls), based on the homeopathic materia medica, the bibliographic references recognised by ANVISA, clinical and/or toxicological studies, pathogenesis or scientific journals.
4.2 Pharmacodynamics: description of the method of action of the drug and/or each of its active ingredients, according to the relevant therapeutics, depending on the category into which it falls.
4.3 The therapeutic indication claimed for the product must be proved by the sending of copies of cited bibliographic references.
a) The claimed therapeutic indication of the drug as a whole can be based on the individual indication of each component, with incompatibilities between the components being observed.
b) For homeopathic drugs, each active ingredient must be entered in at least two homeopathic materia medica.

5. FOR IMPORTED PRODUCTS the following must be submitted in addition to the requirements above:

5.1 Copy of the valid GMPQC certificate issued by ANVISA for the manufacturing company, per production line. If ANVISA has not yet inspected the manufacturing company, proof of an application for sanitary inspection to ANVISA will be accepted, accompanied by the good manufacturing practice for pharmaceutical products certificate for each production line issued by the body responsible for Sanitary Surveillance in the manufacturer's country of origin.
5.2 FOR PRODUCTS IMPORTED IN BULK OR IN THEIR PRIMARY PACKAGING: A copy of the GMPQC certificate issued by ANVISA to the company applying for registration relating to the production line that is the source of the importation in bulk; or a copy of the inspection request memorandum for the purposes of the issuing such certificate. This memorandum will be valid if the company was SATISFACTORY at the last GMPQC inspection.
5.3 Manufacturing company’s permit to market the product in Brazil, or justification for the absence of this document.
5.4 Copy of the certificate of registration of the drug issued by the sanitary authority in the country of origin, or equivalent document.
5.5 Methodology for the physico-chemical, chemical and microbiological quality control to be carried out by the importer, in accordance with the pharmaceutical form of the product (in bulk, in primary packaging and/or final).

5.6 Where it is necessary to import samples for the performance of stability studies, an import permit must be requested from ANVISA.
5.7 The expiry date of products imported in bulk starts from the date of manufacture of the product abroad and not the date of packaging in Brazil, and the expiry date registered with ANVISA must be complied with.
5.8 All other standards in force for imported products must be complied with.
6. The documentation that forms the registration of the product, such as production and quality control reports and information contained on labels, leaflets and packaging, must be in Portuguese in accordance with the legislation in force. Official documents in any other language used for registration purposes must be accompanied by a sworn translation in the form required by law. Documents that contain results of analytical tests or clinical studies, together with copies of bibliographic references, can be submitted in English or Spanish; sworn translations must be provided for all other languages.
7. The technical and legal documentation relating to all of the production sites must be sent, if the company is applying for the registration of a drug produced on more than one production site at the same time.

Appendix III
GUIDE FOR MAKING POST-REGISTRATION CHANGES, ADDITIONS, NOTIFICATIONS AND FOR DYNAMISED DRUGS

1. GENERAL CONSIDERATIONS

The aim of this guide is to classify changes and additions in the post-registration stage of dynamised drugs and set out the documentation and tests required by ANVISA.

Each change, addition, notification or cancellation must be filed separately, accompanied by the relevant documentation.

For changes and additions not covered in this Guide or that do not meet any of the criteria set out, it is up to ANVISA to set out the tests and documentation that must be submitted.

The ANVISA recommendations for post-registration changes for dynamised drugs will be made available on the agency's web site.

2. POST-REGISTRATION CHANGES

2.1 Change in trade name

The following documentation will be required for changes to the trade name of dynamised drugs that have already been registered:

2.1.1 original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.1.2 FP1 and FP2, duly completed;
2.1.3 technical justification relating to the application, as set out in the legislation in force;
2.1.4 declaration of non-marketing of the product, if applicable;
2.1.5 new leaflet (or pamphlet), label and/or cartouche layouts, appropriate to the new trade name.

2.2 Extension of the expiry date

The following documentation will be required to extend the expiry date of dynamised drugs that have already been registered:

2.2.1 original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.2.2 FP1 and FP2, duly completed;
2.2.3 technical justification relating to the application;
2.2.4 Technical report with the results and assessment of the concluded long-term stability test for the lowest dynamisation for each pharmaceutical form, if applicable, in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.2.5 new leaflet (or pamphlet), label and/or cartouche layouts, appropriate to the new expiry date.
2.2.6 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.
2.2.7 [sic]

2.3 Changes to storage instructions

The following documentation will be required for changes to the storage instructions for dynamised drugs that have already been registered:

2.3.1 original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.3.2 FP1 and FP2, duly completed;
2.3.3 technical justification relating to the application;
2.3.4 technical report with the results and assessment of the long-term stability test, if applicable, in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.3.5 new leaflet (or pamphlet), label and/or cartouche layouts, appropriate to the new storage instructions.

2.4 Change in manufacturer/supplier of the active ingredient

This section deals with the replacement of the manufacturer of the active ingredient given at the time of registration. The following documentation, to be sent by the company, will be required:

2.4.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.4.2 FP1 and FP2, duly completed;
2.4.3 Technical justification relating to the application;
2.4.4 For mother tinctures: proportioning of the characteristic chemical component (marker) that identifies the mother tincture, by means of pharmacopoeic or validated methodology;
2.4.5 Production report, in accordance with the legislation in force, or justification for the absence of this document;
2.4.6 Technical report with the results and assessment of the accelerated stability test relating to a batch of the lowest dynamisation for each pharmaceutical form, if applicable, in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, OR justification for the absence of this document;
2.4.7 Document issued by the manufacturer of the active ingredient:
2.4.7.1 General information about the manufacturing company, with full address of the production site of the active ingredient;
2.4.7.2 Method of obtaining the active ingredient and bibliographic references;
2.4.7.3 Specifications, quantification and limits of the principal contaminants;

2.4.7.4 Quality control methodology for the active ingredient;
2.4.7.5 Copy of the Analysis Certificate supplied by the manufacturer of the active ingredient;
2.4.7.6 Proof that the supplying company has satisfactory status with the GGIMP (holds GMP certification), OR justification for the absence of this document;
2.4.8 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

The documentation to be issued by the manufacturer of the drug must be submitted on the manufacturing company's headed paper.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

2.5 Change in production site

Changes to the production site are deemed to be those related to the change of address of the entire production line for a drug.

Beforehand, the company must notify the production of a pilot batch, in accordance with the GUIDE FOR THE NOTIFICATION OF PILOT BATCHES, at the new production site, except for imported products.

The following documentation will be required:

2.5.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.5.2 Copy of the Operating Permit for the new production site;
2.5.3 Copy of the company’s Operating Licence and/or current Sanitary Licence;
2.5.4 Copy of the valid Technical Responsibility Certificate, issued by the Regional Pharmacy Council;
2.5.5 Declaration of the formalisation of the provision of service signed by the legal representatives and technical managers of the companies involved, if applicable;
2.5.6 FP1 and FP2, duly completed;
2.5.7 Technical justification relating to the application;
2.5.8 Location of the new facilities;
2.5.9 Good Manufacturing Practice and Quality Control (GMPQC) certificate for the production line for the product in question, issued by ANVISA for the new production site;
2.5.10 Declaration by the applicant company stating that the production and quality control processes remain unchanged, pursuant to Decree no. 79094 of 05 January 1977 and art. 15 of Law no. 6360 of 23 September 1976, if applicable;
2.5.11 Technical reports and all documentation in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs, if there is any change in the production and/or quality control process. In this case, also apply for a change in the production process of the drug.
2.5.12 Technical report with the results and assessment of the accelerated stability test, for each pharmaceutical form, in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.5.13 New leaflet (or pamphlet), label and/or cartouche layouts, with identification of the new production site.
2.5.14 FOR IMPORTED PRODUCTS:

a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

2.6 Changes in inert ingredients (excipients)

This section deals with changes in the inert ingredient(s) of the registered formula (for each pharmaceutical form, if applicable).

The following documentation will be required:

2.6.1 original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.6.2 FP1 and FP2, duly completed;
2.6.3 technical justification relating to the application;
2.6.4 description of the complete formula, with description of the inert ingredients in accordance with the Common Brazilian Name (DCB), Common International Name (DCI) or the name described in the Chemical Abstract Service (CAS), in that order of priority;
2.6.5 description of the quantity of each substance expressed using the metric system or standard unit, with indication of its function within the formula and the respective quality specification reference described in the Brazilian Pharmacopoeia or other official codes authorised by the legislation in force;
2.6.6 copy of the full production and quality control report for a batch of each pharmaceutical form that will contain the changed inert ingredient;
2.6.7 Documentation and additional information about Transmissible Spongiform Encephalopathy, in accordance with the legislation in force, or justification for the absence of this/these document(s);
2.6.8 Technical report with the results and assessment of the accelerated stability test relating to a batch of each pharmaceutical form, in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.6.9 Preliminary results of a long-term stability study on each pharmaceutical form, in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.6.10 Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA for the production line on which the inert ingredient is manufactured, OR justification for the absence of this document;
2.6.11 New leaflet (or pamphlet), label and/or cartouche layouts, appropriate to the new formula.
2.6.12 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested is not confirmed.

2.7 Changes in the production process of the drug

The following are deemed to be changes to the production of the drug:
a) Changes in the design, principle of operation and capacity of equipment, with the exception of equipment used solely for packaging and/or
b) Changes in stages of the production process and/or in the process itself;
c) Changes in the method or concentration of impregnation of active ingredients.

The following documentation and proofs will be required:

2.7.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.7.2 FP1 and FP2, duly completed;
2.7.3 Technical justification relating to the application;
2.7.4 A copy of full production and quality control reports (in accordance with the legislation in force for product registration), including a copy of the production sequence; detailed production process and process control relating to a batch of each presentation of the product, for each pharmaceutical form.
2.7.5 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.7.6 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.7.7 If stages of production are outsourced, a copy of the notification of the outsourcing contract approved by GGIMP/ANVISA must be attached;
2.7.8 New leaflet (or pamphlet), label and/or cartouche layouts, or justification for the absence of these documents.
2.7.9 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

2.8 Change in batch size

This section deals with increases or reductions in the registered batch size.

It applies to major changes or changes equal to ten times the registered batch size as long as the capacity of the equipment used, the principles of operation and the production process remain the same.

The following documentation will be required:

2.8.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.8.2 FP1 and FP2, duly completed;
2.8.3 Technical justification relating to the application;
2.8.4 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I.

2.8.5 Equipment used in the manufacture of the drug, with details of maximum individual capacity;
2.8.6 Definition of the industrial batch size and criteria for identification of the batch;
2.8.7 Technical report with the results and assessment of the stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.8.8 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

2.9 Change in potency of active ingredient(s)

This applies to changes in the potency of one or more active ingredient(s) of a registered product, as long as the pharmaceutical form, presentation, indication and trade name of the drug remain the same.
The following documentation will be required:

2.9.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.9.2 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I.
2.9.3 FP1 and FP2, duly completed;
2.9.4 Technical justification relating to the application;
2.9.5 Technical reports in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs;
2.9.6 New leaflet (or pamphlet), cartouche and label layouts appropriate to the new formulation, in accordance with the legislation in force.
2.9.7 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

2.10 Change in the owner of the registration of the drug

This applies when the ownership of the product registration changes, due to merger, demerger, incorporation or succession of companies.
The following documentation will be required:

2.10.1 Application forms FP1 and FP2, duly completed;
2.10.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU));
2.10.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I.
2.10.4 Technical justification relating to the application;

2.10.5 Declaration by the applicant company stating that the requirements previously examined remain unchanged pursuant to Decree no. 79094 of 05 January 1977 and art. 15 of Law no. 6360 of 23 September 1976;
2.10.6 Certified true copy of the registration and any changes/additions and renewal (if applicable) for each presentation;
2.10.7 Copy of the Operating Permit;
2.10.8 Copy of the operating licence or current Sanitary Licence;
2.10.9 New leaflet (or pamphlet), cartouche and label layouts, in accordance with the legislation in force;
2.10.10 Certified true copy of the legal document formalising the merger, demerger, incorporation or succession;
2.10.11 Location of the new facilities (only if the production site is changing);
2.10.12 WHEN THERE IS CHANGE IN PRODUCTION SITE: technical report in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs;
2.10.13 Copy of the good manufacturing practice and quality control (GMPQC) certificate issued by ANVISA for the production line on which the drug is manufactured;
2.10.14 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

2.11 Change in packaging for the sole purpose of division

This applies to cases in which the primary and secondary packaging is replaced, with the other characteristics and properties of the product (production process, pharmaceutical form, concentration, quantity of pharmacotechnical unit registered and presentation) remaining unchanged.
The following documentation will be required:
2.11.1 Technical justification relating to the application;
2.11.2 Application forms FP1 and FP2, duly completed;
2.11.3 Proof of exemption for the payment of the sanitary surveillance inspection fee – exempt Sanitary Surveillance Form (tax payment form (GRU));
2.11.4 New label, primary packaging and secondary packaging layout mock-up. If applicable, the primary packaging mock-up must allow for the viewing of the mechanism that makes division possible (perforation, dotted line, etc.).
2.11.5 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, or justification for the absence of this document;
2.11.6 Preliminary results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, or justification for the absence of this document;
2.11.7 Leaflet (or pamphlet) layouts and information on the quantity of leaflets (or pamphlets) that will accompany each original package for divisible packs;
2.11.8 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

2.12 Change in manufacturer/supplier of the inert ingredient (excipient)

This section deals with the replacement of the manufacturer of the inert ingredient (excipient) given at the time of registration.
The same production and quality control process must be maintained.
The following documentation, to be sent by the company, will be required:
2.12.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
2.12.2 FP1 and FP2, duly completed;
2.12.3 Technical justification relating to the application;
2.12.4 Technical report with the results and assessment of the stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.12.5 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
2.12.6 Documentation issued by the manufacturer of the inert ingredient;
2.12.6.1 General information about the company manufacturing the inert ingredient, with full address of the production site;
2.12.6.2 Specifications, quantification and limits of its principal contaminants;
2.12.6.3 Send additional information in accordance with the legislation in force on the control of Transmissible Spongiform Encephalopathy, or justification for the absence of this document;
2.12.6.4 Copy of the Analysis Certificate provided by the manufacturer of the inert ingredient;
2.12.6.5 Proof that the supplying company has satisfactory status with the GGIMP (has a GMP certificate), OR justification for the absence of this document;
2.1.7 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

The documentation to be issued by the manufacturer of the inert ingredient must be submitted on the headed paper of the producing company.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3 POST-REGISTRATION ADDITIONS

3.1 Addition of a new commercial presentation

This section deals with the registration of new presentations of a product already registered, in which:
a) only the quantity or volume of the pharmacotechnical unit registered has changed, or accessories have been added/removed;
b) the concentration, pharmaceutical form and primary packaging remain unchanged;
c) the same equipment is used, with the exception of the equipment used for packaging only;
d) the same standard operating procedures and controls are used and the same formulation and production process remain.

The new registration granted and published in the Brazilian Official Journal does not cancel the registration of the previous presentation. If the company has no interest in the old presentation, it must request the cancellation of the registration.

The following documentation will be required:
3.1.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.1.2 FP1 and FP2, duly completed;
3.1.3 Technical justification relating to the application;
3.1.4 Leaflet (or pamphlet), label and cartouche layouts relating to the new presentation;
3.1.5 The GTIN code(s) for all of the presentations;
3.1.6 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by ANVISA to the manufacturing company. If ANVISA has not yet inspected the manufacturing company, proof of an application for an out of zone inspection will be accepted, accompanied by the GMPQC certificate for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the GMPQC certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.
ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.2 Addition of a new divisible commercial presentation
This section deals with the registration of new divisible presentations of a product already registered, in which:
a) changes have been made to the primary and secondary packaging of the product, and changes may or may not have been made to the quantity or volume of the pharmacotechnical unit registered;
b) the concentration and pharmaceutical form remain unchanged;
c) the same equipment is used, with the exception of the equipment used for packaging only;
d) the same standard operating procedures and controls are used and the same formulation and production process remain.
The new registration will not cancel the registration of the previous presentation. If the company has no interest in the old presentation, it must request the cancellation of the registration.
The following documentation will be required:
3.2.1 Application forms FP1 and FP2, duly completed;
3.2.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU));
3.2.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I.
3.2.4 Technical justification relating to the application;
3.2.5 Label and packaging layouts relating to the new commercial presentation. If applicable, the primary packaging mock-up must allow for the viewing of the mechanism that makes division possible (perforation, dotted line, etc.);
3.2.8 [sic] Leaflet (or pamphlet) layout and information about the quantity of leaflets (or pamphlets) that will accompany each original package for divisible packs;
3.2.6 The GTIN code(s) for all of the presentations;
3.2.7 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.
ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.3 Addition of new packaging

This section relates to the registration of new packaging for a product that has already been registered, in which:
a) the concentration and pharmaceutical form remain unchanged;
b) the same equipment is used, with the exception of the equipment used for packaging only;
c) the same standard operating procedures and controls are used and the same formulation and production process remain.

The new registration granted and published in the Brazilian Official Journal does not cancel the previous registration. If the company has no interest in the old packaging, it must request the cancellation of the registration.

The following documentation will be required:

3.3.1 original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.3.2 FP1 and FP2, duly completed;
3.3.3 technical justification relating to the application;
3.3.4 technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.3.5 preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.3.6 description of the specifications of the primary packaging material;
3.3.7 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.
ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.4 Addition of a new pharmaceutical form already approved in Brazil

This section deals with the addition of a new pharmaceutical form for a product that has already been registered.
The following documentation will be required:

3.4.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.4.2 FP1 and FP2, duly completed;
3.4.3 Technical justification relating to the application;
3.4.4 Full technical report in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs;
3.4.5 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.4.6 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;

3.4.7 Additional information and documents about Transmissible Spongiform Encephalopathy, in accordance with the legislation in force, OR justification for the absence of these documents;
3.4.8 New leaflet (or pamphlet) label and/or cartouche layouts, in accordance with the legislation in force;
3.4.9 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.5 Addition of a new therapeutic indication not contained in the literature

This section deals with the addition of a new therapeutic indication for a product that has already been registered, that is not considered in the literature – materia medica, Anthroposophic Codex, Committee C or D monographs, etc. (as applicable). The same potencies of active ingredients, pharmaceutical form, presentation and production process must be retained.
The following documentation will be required:

3.5.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.5.2 FP1 and FP2, duly completed;
3.5.3 Technical justification relating to the application;
3.5.4 Documentation relating to the clinical or pre-clinical study, pathogenesis, toxicological study or information in the scientific literature that justifies the proposed new indication, including bibliographic references and copies;
3.5.5 New label, cartouche and leaflet (or pamphlet) layouts;
3.5.5 [sic] FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.6 Addition of a new therapeutic indication already contained in the literature

This section deals with the addition of a new therapeutic indication for a product that has already been registered, that is already considered in the literature - materia medica, Anthroposophic Codex, Committee C or D monographs, etc. (as applicable) – and was not requested at the time of registration. The same potencies of active ingredients, pharmaceutical form, presentation and production process must be retained.
The following documentation will be required:

3.6.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.6.2 FP1 and FP2, duly completed;
3.6.3 Technical justification relating to the application;
3.6.4 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;
3.6.5 Documentation relating to the proof of the claimed therapeutic indication: bibliographic references and copies. The new indication must be confirmed with inclusion in at least two references;
3.6.6 New label, cartouche and leaflet (or pamphlet) layouts;
3.6.7 FOR IMPORTED RPODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.7 Addition of a new pharmaceutical form in Brazil

This section deals with the addition of a new pharmaceutical form in Brazil for a product that has already been registered with the same therapeutic indication.
The following documentation will be required:

3.7.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.7.2 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;
3.7.3 FP1 and FP2, duly completed;
3.7.4 Technical reports and all documentation in accordance with the legislation in force that sets out provisions on the registration of new drugs;
3.7.5 Justification for the application;
3.7.6 New cartouche, label and leaflet (or pamphlet) layouts, in accordance with the legislation in force;
3.7.7 The GTIN code(s) for all presentations;
3.7.8 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.8 Addition of a production site

This relates to adding a production site to the site already registered.

Beforehand, the company must notify the production of a pilot batch in accordance with the current GUIDE FOR THE NOTIFICATION OF PILOT BATCHES (except for imported products).
The following documentation will be required:

3.8.1 Copy of the Operating Permit for the new production site published in the Brazilian Official Journal;
3.8.2 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.8.3 Copy of the Operating Licence for the new production site and/or valid Sanitary Licence;
3.8.4 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;
3.8.5 Copy of the valid Technical Responsibility Certificate, issued by the Regional Pharmacy Council;
3.8.6 Declaration of formalisation of the service provision signed by the legal representatives and technical managers of the companies involved, if applicable;
3.8.7 FP1 and FP2, duly completed;
3.8.8 Justification relating to the application;
3.8.9 Location of the new facilities;
3.8.10 Declaration from the applicant company stating that the production and quality control processes remain unchanged, pursuant to Decree no. 79094 of 05 January 1977 and art. 15 of Law no. 6360 of 23 September 1976, if applicable;
3.8.11 Technical reports and all documentation in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs, if there is any change in the production and/or quality control process. In this case, also apply for a change in the production process of the drug;
3.8.12 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.8.13 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.8.14 New leaflet (or pamphlet), label and/or cartouche layouts, identifying the new production site in accordance with the legislation in force;
3.8.15 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.9 Addition of a manufacturer/supplier of an active ingredient

This section deals with the addition of another manufacturer of the active ingredient to the manufacturer given at the time of registration.
The addition of an active ingredient manufacturer will be permitted up to a maximum of three manufacturers, including those already given in the initial registration.
The following documentation will be required:

3.9.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.9.2 FP1 and FP2, duly completed;
3.9.3 Technical justification relating to the application;
3.9.4 Declaration from the applicant company stating that the production and quality control processes remain unchanged, pursuant to Decree no. 79094 of 05 January 1977 and art. 15 of Law no. 6360 of 23 September 1976, if applicable;
3.9.5 Technical reports and all documentation in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs, if there is any change in the starting point (relating to the raw material and the production process) and/or quality control. In this case, also apply for a change in the production process of the drug;
3.9.6 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.9.7 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.9.8 Documentation to be issued by the manufacturer of the active ingredient:
3.9.8.1 General information about the manufacturing company(ies), with full address of the production site of the drug;
3.9.8.2 Specifications of the active ingredient;
3.9.8.3 Copy of the Analysis Certificate provided by the manufacturer of the drug, with references. For active ingredients not described in official compendia, the duly validated analytical method must also be submitted;
3.9.10 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

The documentation to be issued by the manufacturer of the drug must be submitted on the headed paper of the producing company.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.10 Addition of a manufacturer/supplier of an inert ingredient (excipient)
This section deals with the addition of another manufacturer of an inert ingredient (excipient) to the manufacturer given at the time of registration.
The addition of an inert ingredient manufacturer will be permitted up to a maximum of three manufacturers, including those already given in the initial registration. The same production and quality control process must be retained.
The following documentation, to be sent by the company, will be required:
3.10.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.10.2 FP1 and FP2, duly completed;
3.10.3 Technical justification relating to the application;
3.10.4 Technical report with the results and assessment of the stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.10.5 Preliminary results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS;
3.10.6 Documentation issued by the manufacturer of the inert ingredient;

3.10.6.1 General information about the manufacturing company, with full address of the production site of the inert ingredient;
3.10.6.2 Specifications, quantification and limits of its principal contaminants;
3.10.6.3 Copy of the Analysis Certificate provided by the manufacturer of the inert ingredient;
3.10.6.4 Proof that the supplying company has satisfactory status with the GGIMP (has a GMP certificate);
3.10.6.5 Send additional information in accordance with the legislation in force on the control of Transmissible Spongiform Encephalopathy, or justification for the absence of this document;
3.10.7 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;
b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

The documentation to be issued by the manufacturer of the inert ingredient must be submitted on the headed paper of the producing company.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

3.11 Addition of a brand name

This applies when a drug was registered with the official nomenclature, and the company wishes to refer to it by a trade name (brand or “nickname”).
The following documentation will be required:
3.11.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
3.11.2 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;
3.11.3 FP1 and FP2, duly completed;
3.11.4 Copy of the current proof of registration (publication in the Brazilian Official Journal);
3.11.5 Proof of marketing of the product OR justification for the absence of this document;
3.11.6 Justification relating to the application.

4. POST-REGISTRATION NOTIFICATIONS

4.1 Temporary suspension of production

ANVISA must be notified of any temporary suspension of production at least 180 days before the stopping of production, except in emergencies, of a registered product, including at the time of requests for temporary archiving of the process that does not imply the cancellation of its registration.
The following documentation will be required:

4.1.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
4.1.2 FP1 and FP2, duly completed;
4.1.3 Technical justification relating to the application.

4.2 Resumption of production of a drug

ANVISA must be notified of the resumption of production of a drug when production of a registered product restarts.

4.2.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
4.2.2 FP1 and FP2, duly completed;
4.2.3 Technical justification relating to the application.

4.3 Notification of change to leaflet (or pamphlet) text

This notification is valid for all drugs already registered up to the moment when the first electronic version of the leaflet is sent in accordance with the legislation in force.
The following documentation will be required:

4.3.1 FP1 and FP2, duly completed;
4.3.2 Technical justification relating to the application;
4.3.3 Leaflet layout in accordance with the legislation in force.

4.4 Notification of change to label and/or cartouche

The desired changes must be in accordance with the legislation in force for labelling. The following documentation will be required:

4.4.1 FP1 and FP2, duly completed;
4.4.2 Technical justification relating to the application;
4.4.3 New label and/or cartouche layouts.

4.5 Notification of change in potency of an active ingredient
This applies to a change in the potency of one or more active ingredient(s) in a registered drug in order to bring the product into compliance with the legislation in force, as long as the pharmaceutical form, presentation and indication of the drug remain unchanged.
The following documentation will be required:
4.5.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
4.5.2 FP1 and FP2, duly completed;
4.5.3 Technical justification relating to the application;
4.5.4 Technical reports in accordance with the legislation in force that sets out provisions on the registration of dynamised drugs;
4.5.5 Additional information in accordance with the legislation in force about the control of Transmissible Spongiform Encephalopathy, or justification for the absence of this document;
4.5.6 New label, cartouche and leaflet (pamphlet) layouts appropriate to the new formulation, in accordance with the legislation in force;
4.5.7 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, OR justification for the absence of this document;
4.5.8 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, OR justification for the absence of this document;
4.5.9 FOR IMPORTED PRODUCTS:
a) Copy of the Good Manufacturing Practice certificate issued by ANVISA to the manufacturing company OR IN ITS ABSENCE, proof of an application for an out of zone inspection, accompanied by the certificate of Good Manufacturing Practice for Pharmaceutical Products for each production line issued by the body responsible for Sanitary Surveillance in the country of manufacture;

b) Sworn translation of the Good Manufacturing Practice and Quality Control (GMPQC) certificate issued by the body responsible for Sanitary Surveillance in the country of manufacture, or justification for the absence of this document.

ANVISA may at its discretion request additional proof in the event that the equivalence requested above is not confirmed.

4.6 Notification of reduction of the expiry date

This section applies to cases in which the long-term stability studies confirm a shorter expiry date than the date given on registration of the product. In this case, the company must implement the new date immediately.
The following documentation will be required:

4.6.1 Original copy of the proof of payment of the sanitary surveillance inspection fee or proof of exemption if applicable;
4.6.2 FP1 and FP2, duly completed;
4.6.3 Technical justification relating to the application;
4.6.4 Technical report with the results and assessment of the accelerated stability test in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, OR justification for the absence of this document;
4.6.5 Preliminary (or final) results of the long-term stability study in accordance with the current GUIDE FOR THE PERFORMANCE OF STABILITY STUDIES ON DYNAMISED DRUGS, OR justification for the absence of this document;
4.6.6 Pharmacosurveillance report, if applicable;
4.6.7 New leaflet (pamphlet), cartouche and label layouts appropriate to the new expiry date.

4.7 Supplement

This is all and any supplement to the process, not required formally, that is limited to the enhancement of the knowledge of the subject of the process, that does not result in any declaration different from that previously applied for.
Necessary documentation:
4.7.1 Cover sheet;
4.7.2 Justification;
4.7.3 Documentation to be added.

4.8 Submission of missing documentation

This is the submission of all and any documents omitted from a previously filed application, whether formally required or not.
Necessary documentation:
4.8.1 Cover sheet;
4.8.2 Justification;
4.8.3 Documentation to be added.

5. POST-REGISTRATION CANCELLATION

5.1 Cancellation of registration of the presentation of the drug by request

The partial cancellation of the registration by request consists of the cancellation of the registration of certain presentations of the drug.
The following documentation will be required:

5.1.1 FP1 and FP2, duly completed;
5.1.2 Justification relating to the application.

5.2 Cancellation of the registration of the drug by request

The total cancellation of the registration by request consists of the cancellation of the registration of all presentations of the drug.
The following documentation will be required:

5.2.1 FP1 and FP2, duly completed;
5.2.2 Justification relating to the application.

5.3 Cancellation of the registration of the drug due to transfer of ownership
This consists of the cancellation of the registration of all presentations of the drug, due to the merger, demerger, incorporation or succession of companies.
The following documentation will be required:

5.3.1 Application forms FP1 and FP2, duly completed;
5.3.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU)).
5.3.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I.
5.3.4 Technical justification relating to the application;
5.3.5 Certified true copy of the legal document formalising the merger, demerger, incorporation or succession;
5.3.6 Copy of the current registration.

5.4 Reactivation of registration by court order
This relates to the reactivation of a registration previously cancelled or lapsed, or the renewal of which has previously been rejected, by court order.
The following documentation will be required:
5.4.1 Application forms FP1 and FP2, duly completed;
5.4.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU)) or proof of exemption. If applicable;
5.4.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;
5.4.4 Justification relating to the application, containing a certified true copy of the legal document;
5.4.5 Copy of the last publication relating to the registration/renewal of the registration of the product.

6. Temporary archiving

6.1 Temporary archiving of the application
This relates to the request for archiving of a secondary application for a given time, in accordance with the legislation in force, and in view of founded reasons.
The following documentation will be required:
6.1.1 Application forms FP1 and FP2, duly completed;
6.1.2 Technical justification relating to the application;
6.1.3 Detailed schedule relating to the fulfilment of the requirement(s) or justification for the absence of this document.

6.2 Temporary archiving of the process
This relates to the request for archiving of a primary application for a given time, in accordance with the legislation in force, and in view of founded reasons.
The following documentation will be required:
6.2.1 Application forms FP1 and FP2, duly completed;
6.2.2 Technical justification relating to the application;
6.2.3 Detailed schedule relating to the fulfilment of the requirement(s) or justification for the absence of this document.

6.3 Dearchiving of an application

The following documentation will be required:

6.3.1 Copies of the FP1 and FP2 filed as part of the process;

6.3.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU)) or proof of exemption, if applicable;

6.3.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;

6.3.4 Justification for the dearchiving with all relevant clarifications;

6.3.5 Copy of the request for archiving filed by the company;

6.3.6 Copy of the official letter from GGMED/ANVISA with regard to the archiving of the application;

6.3.7 Documentation relating to the complete fulfilment of the requirements set out prior to archiving.

6.4 Dearchiving of a process

The following documentation will be required:

6.4.1 Copies of the FP1 and FP2 filed as part of the process;

6.4.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU)) or proof of exemption, if applicable;

6.4.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;

6.4.4 Justification for the dearchiving with all relevant clarifications;

6.4.5 Copy of the request for archiving filed by the company;

6.4.6 Copy of the official letter from GGMED/ANVISA with regard to the archiving of the application;

6.4.7 Documentation relating to the complete fulfilment of the requirements set out prior to archiving.

7. Appeals

7.1 Appeal for reconsideration of rejection

The following documentation will be required:

7.1.1 Application forms FP1 and FP2, duly completed;

7.1.2 Justification for the application, containing the company's argument and all relevant clarifications and documents;

7.1.3 General information about the company;

7.1.4 Power of attorney, in the event of third-party intervention;

7.1.5 Copy of the publication of the rejection of the application in the Brazilian Official Journal, or justification for the absence of this document;

7.1.6 Copy of the official letter or communication of rejection received by the company, if this exists.

7.2 Appeal against lapse of registration

The following documentation will be required:

7.2.1 Application forms FP1 and FP2, duly completed;

7.2.2 Justification for the application, containing the company's argument and all relevant clarifications and documents;

7.2.3 General information about the company;

7.2.4 Power of attorney, in the event of third-party intervention;

7.2.5 Copy of the publication of the rejection of the application in the Brazilian Official Journal;

7.2.6 Copy of the official letter of lapse received by the company, if this exists.

7.3 Appeal against administrative rejection – Brazilian Public Service Unit (UNIAP)

Applies to applications rejected in the UNIAP register.

The following documentation will be required:

7.3.1 Cover sheet, duly completed;

7.3.2 Justification for the application, containing the company's argument and all relevant clarifications and documents;
7.3.3 General information about the company;
7.3.4 Power of attorney, in the event of third-party intervention;
7.3.5 Copy of the official letter or communication of rejection received by the company, if this exists.

8. Corrections of publication errors

8.1 Correction of publication error - ANVISA
This applies when the publication error was made on the part of ANVISA.
The following documentation will be required:
8.1.1 Application forms FP1 and FP2, duly completed;
8.1.2 Detailed justification for the correction request;
8.1.3 Copy of the previously filed application forms relating to the subject to be corrected;
8.1.4 Copy of the publication in the Brazilian Official Journal relating to the correction.

8.2 Correction of publication error - COMPANY
This applies when the publication error was made on the part of the company.
The following documentation will be required:
8.2.1 Application forms FP1 and FP2, duly completed;
8.2.2 Original copy of the proof of payment of the sanitary surveillance inspection fee (tax payment form (GRU));
8.2.3 Proof of size category of the company in accordance with the legislation in force, except for companies classified as Large Group I;
8.2.4 Detailed justification for the correction request;
8.2.5 Copy of the previously filed application forms relating to the subject to be corrected;
8.2.6 Copy of the publication in the Brazilian Official Journal relating to the correction.

Appendix IV
DYNAMISED DRUG CONSUMER INFORMATION LEAFLET and PAMPHLET

LEAFLET

The order and content of the dynamised drug leaflet must comply with the following:

1 – IDENTIFICATION OF THE DRUG

1.1 Trade name or brand.

1.2 Name of the active ingredients, in accordance with the official nomenclature.

1.3 Pharmaceutical form(s), route(s) of administration and presentation(s).

1.4 Restrictions on use: insert one of the highlighted phrases, as applicable: "Adult use" or "Paediatric use" or "Adult and paediatric use".

1.5 Composition: qualitative and quantitative description for the active ingredients (in accordance with the official nomenclature) and qualitative description for the inert ingredients. For active ingredients, give the dilution (potency)/scale (decimal or centesimal) and preparation method (if applicable). Give the alcohol content, for liquid formulations.

1.6 Weight, volume of liquid or quantity of units, as applicable.

1.7 Identification of the category of the drug. Use the phrases "This is a homeopathic drug" OR "This is an antihomotoxic drug" OR "This is an anthroposophic drug" as applicable.

2 - INFORMATION FOR THE PATIENT

Obligatory and uniform, written in language that will be easily understood by the general consumer.

2.1 Expected action of the drug or **"How does this drug work?"**: describe the actions of the drug in accordance with the findings of homeopathic, anthroposophic or antihomotoxic pharmacodynamics and therapeutics (as applicable).
2.1.1 The terminology used, taken from the materia medica (in the case of homeopathic medicine), the Codex or Committee C (in the case of anthroposophic medicine) and the description of clinical signs, symptoms and conditions must, for better understanding by the reader, be written in current language, with verified synonymy between the original term and its equivalent in current use in clinical medicine. The terminology recommended by the International Classification of Disease, ICD-10, will be used in relation to signs, symptoms and diseases.

2.2 Indications of the drug or **"What is this drug used for?"**: briefly describe what specific clinical situation the drug proposes to treat, specifying whether it is **auxiliary** to the treatment or not.
2.2.1 Obligatory phrase: *"The indication of this drug can only be changed at the doctor's discretion"*.

2.3 Risks of the drug or **"When should I not take this drug?"**: Describe the contra-indications or limitations of the use of the drug. This part of the leaflet should in particular alert the reader with regard to the following:
2.3.1 Warnings: alert to the appearance of new symptoms or exacerbation of current symptoms;
2.3.2 Precautions: In this section, include a warning about the risk of use by non-recommended route;
2.3.3 Intolerances: give, in the form of a warning, information relating to the inert ingredients. The following suggested phrases may be used: "Caution: this drug has an alcohol content of ____ "; "This drug contains ALCOHOL"; "This drug contains LACTOSE"; "Diabetics: this drug contains SUCROSE".

2.4 Include the warning phrases in accordance with the Guide for "Warning Phrases Associated with the Risk Categories of Drugs Intended for Pregnant Women".

2.5 Include the following highlighted expressions:
a) "Tell your doctor if any undesirable reaction occurs"
b) "Tell your doctor if you are taking any other drugs"
c) "Do not take this drug without your doctor's knowledge. It could be dangerous to your health" - for drugs sold on prescription.
d) "Contribute to the treatment: tell the doctor about all of the treatments you have already had or are taking. Listen to your doctor's suggestions, so that his treatment is effective and you have a good quality of life".
e) "Consult your doctor regularly. He can assess the progress of the treatment correctly. Follow his instructions correctly."

2.6 Instructions with regard to newborns, pregnant women, the elderly and diabetics – describe as applicable, or use the phrase *"Studies have not been carried out on these groups of patients"*.

2.7 Warn that incorrect use of the drug can mask or aggravate symptoms. Mention that self-medication can lead to incorrect or doubtful diagnosis.

2.8 Method of use or **"How should I take this drug?"**: Describe how to take the drug. Give details of the suggested dose, describing the dose for each pharmaceutical form with the relevant instructions for use, frequency of administration, duration of the treatment, and its routes of administration.

2.8.1 **"In what form should children and adults take the drug?"** – give specific instructions, if applicable.

2.8.2 Include the following highlighted expressions:
a) "Do not take this drug after its expiry date."
b) "Before taking, check the appearance of the drug." Include a description of the expected appearance of the drug and distinctive organoleptic characteristics that will enable the patient to assess its quality.
c) "Your doctor may change the suggested dose to meet your individual needs."
d) "Follow the method of use correctly. If symptoms persist, seek advice from your doctor."

2.8.3 For drugs sold on prescription, add the following expressions:
a) "Follow your doctor's instructions and always take the correct dose at the correct time, and complete the course of treatment."
b) "Do not stop the course of treatment without your doctor's knowledge."
c) "Take your medication at the recommended times."

2.9 Adverse reactions or **"What side-effects can this drug have?"**: Give the most common types of side-effect and the frequency of adverse reactions to the drug, if applicable; this is compulsory for drugs supplied in 1CH, 2DH or lower dynamisations. If this section is not applicable, use the phrase: *"None yet known".*

2.10 Conduct in the event of an overdose or **"What to do if someone takes a large quantity of this drug at once"** or **"What to do in the event of accidental or intentional ingestion of this drug"**: describe the appropriate action for emergency care, especially for drugs that contain active ingredients in 1CH, 2DH or lower dynamisations.

2.10.1 List the adverse reactions and undesirable effects in the event of an overdose/intoxication, if applicable.
2.10.2 Add the phrase "*In the event of accidental ingestion and/or ingestion above the dose suggested/prescribed by a doctor, or in the event of symptoms that cause illness during the treatment, seek advice from your doctor or pharmacist."*

2.11 Storage instructions and use or **"Where and how should I store this drug?"**: Describe specific instructions for keeping the drug and storage before and after opening the package or preparation. Include the following highlighted expressions:
a) *"Once open, this drug should be consumed within ___ days"* – for drugs the stability of which decreases before their original expiry date once open.
b) "ALL DRUGS SHOULD BE KEPT OUT OF REACH OF CHILDREN".
c) "Protect from sunlight and sources of radiation such as microwave ovens, mobile phones, televisions, etc.".
d) "Store in a cool dry place (15-30°C)".
e) Any other specific storage instructions.

2.12 For homeopathic drugs: Clarification or **"What should I know about this homeopathic drug?"**: add the following obligatory phrases:
a) "Homeopathic drugs are indicated according to the individual needs of each patient, and not for specific diseases."
b) "The dose of the homeopathic drug is determined individually for each patient. Your homeopath may change the dose suggested in this leaflet to meet your needs."

3 – TECHNICAL INFORMATION FOR HEALTH PROFESSIONALS

The information for health professionals must comply with the terminology recommended by the International Classification of Disease, ICD-10, with regard to signs, symptoms and diseases.

3.1 Pharmacological properties: describe the drug with its pharmacodynamic properties based technically and scientifically within the scope of the proposed therapeutics (homeopathic, anthroposophic or homotoxicological).

3.2 Therapeutic indications: describe the therapeutic indications duly registered with ANVISA.

3.3 Contra-indications: describe, if applicable, the specific contra-indications or factors that limit the use of the drug, such as hypersensitivity to the active principles (this is obligatory for 1CH, 2DH or lower dynamisations) or excipients.

3.4 Suggested dose: dose, duration of treatment and routes of administration. Give the maximum daily dose if the dynamisation is such that it could lead to toxic effects if consumed in excess of the limit set.

a) Give details of the dose for specific diseases and special situations, if applicable.
b) Describe the action necessary if a dose is missed, if applicable.
c) Include adjusted doses for elderly patients and other risk groups, if applicable.

3.5 Warnings: describe the warnings, recommendations on the appropriate use of the drug and restrictions.

a) Highlight the risks of taking the drug by a non-recommended route of administration.
b) Give the risk category during pregnancy, including the warning phrases in accordance with the Guide for “Warning Phrases associated with the Risk Categories of Drugs Intended for Pregnant Women,” if applicable.

3.5 [sic] Use in the elderly, children and other risk groups: describe the warnings and recommendations for the appropriate use of the drug for risk groups, if applicable. When this section is not applicable, include the following phrase: *"No studies have been carried out on this group of patients"*.

3.6 Drug interactions: give, in order of severity and/or frequency, the drug interactions with foodstuffs, laboratory examinations, other drugs, tobacco, alcohol, in addition to incompatibilities, with specification of the substances or groups of substances, if applicable. If this section is not applicable, include the following phrase: *"None yet known"*.

3.7 Overdose: describe the general and specific action to take in the event of an overdose; this is obligatory for drugs that contain at least one component in a 1CH, 2DH or lower dynamisation. In this case, include toxicological information about the main chemical constituents that might be present.

3.8 Storage: describe the ambient conditions for keeping/storage of the product.

3.9 Identification of the category of the drug. Use the following phrases: *"This is a homeopathic drug"* OR *“This is an antihomotoxic drug”* OR *“This is an anthroposophic drug”*, as applicable.

4 – Legal statements

a) ANVISA/MS registration number; this must consist of the 13 digits of the registration number as published in the Brazilian Official Journal.
b) Responsible pharmacist and his/her registration number with the regional pharmacy council.
c) Full name and address of the manufacturer and the owner of the registration (with the phrases “manufactured by”, “packaged by” and “distributed by” where applicable).
d) CNPJ no.
e) Telephone number of the company’s Consumer Service Department.
f) Include the following phrases, if applicable:

“Sold on prescription”
“Dispensed on prescription” (for official laboratories).

PAMPHLET

The pamphlet for the dynamised drug must have the same content as required for leaflets, ***EXCEPT*** for the following sections:

2.2 Indications of the drug or **“What is this drug used for?” -** and sub-sections.
3 TECHNICAL INFORMATION FOR HEALTH PROFESSIONALS - and sub-sections.