REGULATION FOR HEALTH REGISTRATION OF DRUGS IN GENERAL

Ministerial Agreement 586

Official Gazette 335 of Dec 07th 2010

Last amendment: March 15th 2014

Status: Valid

GENERAL NOTE:

Are repealed the provisions on the manual process for obtaining health registration for products subject to surveillance and health control that are set out in this regulation.

Repeal given by Ministerial Agreement No. 4119, published in Official Gazette 84 of September 19, 2013.

MINISTER OF PUBLIC HEALTH

Considering:

That the Constitution of the Republic of Ecuador provides:

"Art. 32. Health is a right guaranteed by the Government which is linked to the exercise of other rights, including the right to water, food, education, physic culture, labor, social security, healthy environments and others aspects that support the good life ";

"Art. 361. The Government shall exercise leadership of the system through the national health authority, will be responsible for formulating the national health policy and shall regulate, regulate and control all health-related activities and the functioning of the sector entities. ";

That the Health Law provides:

"Art. 137. They are subject to health registration processed foods, additives, food, medicine in general, nutraceuticals, biological products, natural processed products for medicinal use, homeopathic products, dental products; medical devices,....":

"Art. 138. The national health authority through its competent authority, the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Perez, which works as

decentralized, institution, shall suspend, cancel or re-enrolled health registration certificate, subject to compliance with the procedures, requirements and deadlines specified in this Act and its regulations according to the guidelines and regulations issued by the national health authority ... ";

That, by Ministerial Agreement No. 00000236 published in Official Gazette No. 188 from May 7th 2010, it was issued the Regulation of Health Registry for Medicines in General, reform still needed to have a legal basis according to the current reality to make efficient the administrative and technical veterinary procedures; and,

In exercise of the legal powers granted by Articles 151 and 154, paragraph 1 of the Constitution of the Republic of Ecuador and Article 17 of the Statute of the Legal System for the Administration of the Executive Branch.

Determines:

ISSUE THE SUBSTITUTE REGULATION FOR HEALTH REGISTRATION FOR MEDICINES IN GENERAL

Note: Errata included, published in Official Gazette 374 of January 31st 2011

CHAPTER I

Health registration

Art. 1. For the production, import, export, marketing, supply and sale of medicine in general, it is mandatory to obtain the corresponding health registration.

Health registration certificate will be issued on behalf of a holder who will be responsible for its use and will have a single format approved by the national health authority.

Art. 2. As provided in Art. 138 of the Organic Law of Health, the National Institute of Hygiene and Tropical Medicine "Dr. Leopoldo Izquieta Perez (INH)", is the technical agency responsible to grant, suspend, cancel or re-enroll the certificate of health registration, according to the guidelines and standards issued by the national health authority.

Art. 3. The entry in the health registration as well as quality control analysis post-registration, are subject to payment of the amounts established by law and regulations.

Note: Article amended by Ministerial Agreement No. 1090, published in Official Gazette 729 of June 21st 2012.

Note: Agreement No. 1090 repealed and Article amended by Ministerial Agreement No. 2883, published in Official Gazette 889 of February 8th, 2013.

Art. 4. Regulatory approval will be granted within a maximum period of 15 days, upon completion of all the requirements established by law, these rules and regulations established by the national health authority.

CHAPTER II

Requirements for Health Registration

Art. 5. To get the health registration of a drug, the manufacturer or legal representative must submit to INH an individual application for each pharmaceutical form and concentration or active ingredient, the original and a copy.

Each application must contain the following:

a) The generic or International Nonproprietary Name (INN) of the drug and the commercial name if any;

b) Qualitative and quantitative formula, with active ingredients and excipients related to 100 g or 100 mi, or by unit dosage form, expressed in units of the International System (SI), or conventional of the activity, when previous not available;

c) The generic name of the active ingredients of the formula as they are in the list of International Nonproprietary Names (INN) for pharmaceutical substances published by the World Health Organization (WHO).

In case you do not appear or in this list, indicate the proposed WHO name according with existing procedures, including the general accepted name for the authorized organism to formalize such names in the country: British Approved Name (BAN) United States Adopted Name (USAN), Japanese Accepted Name (JAN) Italian Denominazione Comune (DCIT) Denomination Comune Francaise (DCF), as appropriate, translated into Spanish according to the recommendations of the DCI to standardize the Spanish version;

d) The chemical name according to Chemical Abstracts Service (CAS) and the registration number in the CAS, as stated in Annex 3 of the DCI duly crossed with the generic name;

e) Pharmaceutical form and description; if powder to reconstitute, declare the description of both, the powder and the reconstituted formula.

f) Description of the primary and secondary containers, including physical and chemical specifications as appropriate;

g) Package contents expressed in units of the International System (SI) and / or number of units of the pharmaceutical form;

h) Forms of presentation;

i) Name of manufacturer or the holder of the product;

j) Name of city and country of manufacturer and the holder of the product;

k) Name of the packer and / or conditioner if it is different from the manufacturer, stating the city and country;

l) The name and full address of the pharmaceutical establishment and the natural or legal person who is the responsible one who is requesting the health registration;

m) Batch number, manufacture date, expiration date and shelf life of medicine;

n) Route of administration; and,

o) Original signature of the responsible pharmaceutical chemist or pharmaceutical biochemical for the product and the legal representative or attorney, on the request.

Art. 6. Attached the following requirements to the application. These requirements should be submitted properly identified, foliated and signed both physical and in magnetic as a scanned file, in accordance with the instructions designed for this purpose:

a) A certified copy of valid operating license, granted by the competent health authority;

b) Notarized copy of the incorporation of the corporate person that requests the registration, duly legalized;

c) Valid authentic Certificate of Good Manufacturing Practices (GMP), which includes the pharmaceutical form for which they are requesting the heath registration. For imported medicines, notarized copy of BPM (GMP) certificate issued by the competent authority of the country of origin of the manufacturer should not be declared on the Certificate of Pharmaceutical Product (CPF) or Certificate of Free Sale (Counter Drug) (CLV);

d) Notarized copy of the current appointment of the legal representative or power of attorney registered in the Registro Mercantil (Merchants Registry), and copy of RUC (Tax ID), in case of legal persons; for individuals copy of identity card or citizenship card and the RUC (Tax ID);

e) Notarized copy of the professional qualification of the responsible chemical or biochemical pharmacist, registered in the Ministry of Public Health and copy of the identity card or citizenship;

f) The molecular and graphic formula according to the DCI, USAN, the United States Pharmacopeia (USP), or Merck Index:

g) Original of the duly legalized authorization of the owner of the product to apply for health registration, where appropriate;

h) Notarized copy of the authorization, duly authenticated power or contract for the development of the product by a domestic laboratory, when the holder is another laboratory;

i) Original of the authorization of the owner of the product to use the relevant technical documentation in the case of marketing of a same product between agreed two or more co-responsible laboratories that where responsible of the research and product development;

j) Interpretation of batch code; signature, name and title of the responsible pharmaceutical chemist or pharmaceutical biochemical in original;

k) Original certificate of analysis of the batch of the finished product subject of these proceedings for health registration, with original signature, name and title of the responsible pharmaceutical chemist or pharmaceutical biochemical;

l) Original certificate of analysis of standards or benchmarks used in the control tests of the pending medication, with original signature, name and position of the responsible pharmaceutical chemist or pharmaceutical biochemical;

m) Certification that the additives and colorants (color index) used, are authorized to drug use in the official list of the Food and Drug Administration, FDA; specifying the code and the date of the document;

n) Study of stability of the product, in original, with signature, name and position of the responsible chemical pharmacist or biochemical pharmacist of the laboratory that conducted the study:

1. Long-term studies conducted in experimental moisture and temperature conditions corresponding to the climate zone IV are accepted (1CH Guide) or United States of North American Pharmacopeia (USP), as appropriate, with duration equal to the period of the proposed shelf life.

2. Accelerated studies are accepted if conducted at 40 degrees Celsius (plus or minus) 2 degrees Celsius and 75% (plus or minus) 5% relative humidity, with a duration of six months together with a study on the humidity and temperature at corresponding area IV climate, with duration of 12 months upon entry of the product to the registration process.

3. Any variant accelerated stability method indicated in this paragraph shall be supported by a method of stability internationally recognized as valid, based on the Arrhenius equation;

o) Specifications of the finished product, in the original document, with the name and title of the responsible pharmaceutical chemist or pharmaceutical biochemical;

p) If a product from an alternate manufacturer, must be presented: justification of pharmaceutical equivalence by presenting comparative dissolution profiles between product produced by alternate manufacturers and the main manufacturer (according to instructions) and corresponding statistical evaluation using the similarity factor F2 or equivalent method and studies of long-term stability for zone IV;

q) Description of the nature of the primary and / or secondary container and physicochemical specifications thereof;

r) Reference pattern or the active ingredients packaged in glass vial with term not less than six months, labeled with chemical name (INN), lot number, expiration and power, indicating whether it is primary or secondary;

s) Technical-analytical documentation and dosage in Spanish, with the option to have it also in English, containing the following:

1. Qualitative and quantitative formula with active ingredients and excipients, related to 100 g or 100 ml, or pharmaceutical form unit expressed in SI units (International System units) or conventional of the activity in the absence of the above.

2. Certificate of quality control analysis with specifications for raw materials quality and purity limits, in the original document, with signature, name and title of a responsible chemic pharmacist or biochemical pharmacist:

t) Test procedures for the identification, quantification and evaluation of the physical, chemical, chemical, biological, microbiological, pharmacological characteristics of the pharmaceutical form as support of the finished pharmaceutical product, which also include the following as the case requires:

- Studies of in vitro equivalence: dissolution test.

- Studies of in vivo (live) Equivalence only required for products of high health risk (in accordance to the WHO classification), considering the bio-extensions and Biopharmaceutical Classification System:

- Bioequivalence (pharmacokinetic studies).

- Pharmaceutical-dynamic studies.

- Comparative clinical trials.

For the above, the list of active ingredients contained in the pharmaceutical products shall be set, for the products that bioequivalence studies will be requested.

The INH will display the formal list of active ingredients that require the submission of such studies for the health registration process and their reference products.

The pharmacological procedures should be related to the therapeutic use the product is meant for.

For biological products the official method of analysis should be sent;

u) Description of procedures of internal quality control during the manufacturing process;

v) Original product labels of the country from which it is imported and the project labels to be sold in the country, in quadruplicate;

w) Original samples from the same batch number declared in accordance with the provisions of the literal m) of the preceding article; these samples must have an expiration date no less of six months;

x) Brief description of the product development process. The manufacturing process must be done by the same manufacturer;

y) Current pharmacological and clinical documentation in Spanish and English version can also be attached, showing: the validity of the therapeutic indications proposed by the manufacturer for the pending product.

The aforementioned documents are confidential and will be used exclusively for the processing of the health registration; and.

z) Proof of payment of the value corresponding to the amount of the health registration, according to valid regulations.

The responsible pharmaceutical chemist or pharmaceutical biochemical professional with registration of his/her title in the Ministry of Public Health of Ecuador, shall guarantee with his/her signature all technical documents submitted.

When simultaneously it is submitted to process one substance and dosage form but with different concentrations, technical documents mentioned in this article may be the same.

It is acceptable only one applicant requesting health registration of two drugs with the same formula of composition, pharmaceutical form and presentation provided one is generic and the other branded.

Attached to the application and annexes it is necessarily a control form of the documents that are submitted for the registration process, in which are accurately identify all documents that are attached and the folio or folios of all the submitted documentation. This form shall be signed by the registrant, becoming the statement that the documentation is complete and meets all the requirements of this regulation.

Art. 7. In the case of imported drugs in addition to the requirements mentioned in the previous article, they must attach the "Certificate of Pharmaceutical Product traded Internationally" according to the WHO model or the" Free Sale Certificate "issued by the competent authority of health of the country of origin of the product, stating the complete qualitative and quantitative composition formula, the pharmaceutical form, which ensures that:

1. It is made by a laboratory legally established in the country of manufacture.

2. The manufacturing laboratory complies with good manufacturing practices and is subject to regular supervision by the health authority.

3. The product complies with the technical and legal requirements for the health registration.

4. It is sold freely in the country and that it is not a manufactured product exclusively for export; except in the following cases:

a) The product has been developed exclusively for the treatment of diseases not endemic in the exporting country;

b) The product has been reformulated with a view to improving its stability under weather conditions corresponding to Ecuador;

c) The product has been reformulated to exclude excipients not approved for use in pharmaceutical products in Ecuador;

d) The product has been reformulated to meet a different maximum dosage limit of an active ingredient;

e) The product for commercial reasons is not sold in the country of origin, but has no declaration of health objection by the relevant health authority; and,

f) When the product is manufactured under contract for a pharmaceutical company established legally in Ecuador, in this case the certificate of pharmaceutical product must ensure that it has no health objection to market it in the country of origin.

The existence of one or more of these exceptions must be stated expressly in the Certificate of Pharmaceutical Product (CPF).

In the case of imported products it will be considered valid the certificate of pharmaceutical product or the certificate of free for sale, that is submitted as requirement for the health registration, which will have a term of twenty-four months from the date of issue, in Ecuador, without prejudice to a shorter period established by the health authority of the country of origin of the product that issues the certificate.

It may be included in the same health record, besides the main manufacturer an alternative manufacturer, which must meet the same requirements of this regulation than the main manufacturer.

Note: Article amended by Ministerial Agreement No. 2883, published in Official Gazette 889 from February 8th 2013.

Art. 8. In the case of imported drugs through free zones or distribution centers, it is required to attach a certificate duly legalized in which it is declared that it maintains a warehousing and distribution agreement with the holder of the product; It is also necessary the certificate of good storage practices in force or the operation permit (license) of that establishment, issued by the competent health authority.

Art. 9. In the case of new drugs, the application and annexes shall meet the requirements established in previous articles, and the following:

1. When the product has been researched and developed by the parent company of a laboratory, it must enclose a letter of responsibility issued by the parent company of the laboratory that researched and developed the molecule containing:

1.1 The certification that the research plan is carried out according to the international canons established for this type of research.

1.2 Certification that the product has fully completed its experimental phase according to the plan mentioned in the preceding paragraph and the safety and efficacy results support the intended use.

1.3 Obligation to submit every six months, or sooner if needed, through the representative in Ecuador, the results of pharmacovigilance programs of the parent company, carried out in the next three years from issuing the health product registration which lets to amend or ratify their indications, contraindications, side effects and get relevant information on the safety and therapeutic efficacy of the product. When detected any negative response that exceeds safe limits, the information must be reported immediately to the appropriate health authorities.

2. When the product has been investigated by a subsidiary established in a country other than the Headquarters, a letter of responsibility from the parent company will be presented, which will contain:

2.1 Certification that the subsidiary operates under scientific technical supervision of the parent company.

2.2 Certification that the research plan carried out by the subsidiary in relation to product conforms to the standards of the parent company, and international established for this type of research.

2.3 Certification that the product has fully completed its experimental phase under the plan referred to in the preceding paragraph and the safety and efficacy results support the indicated therapeutic use.

2.4 Commitment to establish a pharmacovigilance system in the country or send pharmacovigilance results of programs of the parent company carried out in the next three years, or sooner if necessary, from issuing health registration, which helps to amend or ratify the indications, contraindications, adverse effects and further information concerning relevant to safety and therapeutic efficacy. Such information should be reported semiannually to the relevant health authorities, except when detected any negative response that exceeds the stated limits of patient safety, which should be reported immediately to the authorities.

3. In the case of a product with more than five years of marketing in foreign markets, with full technical and scientific reference, which is published in international accredited literature, but be new drug in the country, will submit a letter of responsibility from the headquarter containing:

3.1 Commitment to establish and report on the system of pharmacovigilance, as noted in Clause 2.4.

3.2 Certification that the petitioner of the registration is a subsidiary that operates under technical and scientific supervision of the headquarters.

4. In the case of a product developed by a foreign company, not sold by it, but by concession or manufacturing license to another laboratory, letter of responsibility from the parent containing:

4.1 Certificate of the research laboratory of the new active ingredient that it has complied with all phases of experimentation according to the canons of the laboratory, the host country and international ones, established for this type of research and its results on safety and effectiveness support the proposed therapeutic use.

4.1 (sic) Certification and commitment established in sections 2.2 and 2.4 of this article.

5. Products manufactured in Ecuador and developed by a foreign company, sold by the last one, and licensed to the national manufacturing laboratory, must submit a letter of responsibility of the parent company containing:

5.1 The certification that the research plan was done according to the international canons established for this type of research.

5.2 Certification that the product has fully completed its experimental phase according to the plan mentioned to in the preceding paragraph and the safety and efficacy results support the intended use.

5.3 Obligation to submit every six months or sooner if needed, through the representative in Ecuador, the results of pharmacovigilance programs of the parent company, carried out in the next three years from issuing the health registration to the product which helps to amend or ratify their indications, contraindications, side effects and get relevant information on the safety and therapeutic efficacy of the product. When detected any

negative response that exceeds safe limits, the information must be reported immediately to the appropriate health authorities.

6. For a product developed by a multinational and submitted to the procedure by its subsidiary stablished in Ecuador, must submit a letter of responsibility of the parent company containing what was mentioned in the previous paragraph.

7. In the case of new drugs introduced by other laboratories different to the laboratory that developed the innovation must attach:

7.1 Letter of responsibility issued by the holder of the product, ensuring that the safety and efficacy for the intended use is supported by clinical studies, published in the last five years in scientific journals.

7.2 Duly authenticated document in which the health authority of the country of origin of the product certifies that the active ingredient in the pharmaceutical form declared is registered, and when first registered in that country the holder of that product submitted preclinical and clinical trials guaranteeing the safety and efficacy of the product.

7.3 Commitment to submit within a period not exceeding 90 days from the date of issuance of the certificate of health registration, the pharmacovigilance program to be carried out in the Ecuador, to run that program after its official approval, and send corresponding semester reports, during the first three years from the grant of health registration, which will rectify or ratify the indications, contraindications, side effects and obtain relevant information on the safety and therapeutic efficacy of the product. When detect any negative response that exceeds safe limits, the information must be reported immediately to the appropriate health authorities.

Art. 10. Whatever is the origin of the product as new drug, it also needs to be attached:

1. Works of pharmacological and toxicological nature that prove the drug's effects on the various organs and body systems, modalities, destination and excretion, or possible biological activity of the metabolites formed, the (acute, subacute toxic effects and chronic) produced by the drug and any other pharmacological property of interest.

2. Work of clinical nature, with checks and tests in double-blind and other requirements of phase III. If the drug is of foreign origin, a part of the work must have been made in the country of origin or third countries that have recognized scientific research centers.

3. The works, especially those of pharmacological and clinical nature, must have been published in prestigious international scientific journals in the last five years. These papers must be submitted in Spanish. In general, the work should allow the formation of an objective judgment on the therapeutic usefulness of the new drug, as well as their secondary reactions, toxicity, contraindications, precautions and drug interactions.

4. The works that are sent to support a new drug should include information on the passage thereof through the placenta and its effects on the embryo and fetus, elimination of medicine in the milk, its effect on lactation and infant.

5. Works on the teratogenic effects of the new drug that meet the following minimum requirements:

5.1 The tests must at least have been made on three species of mammals, one of which should not be rodent or lagomorph.

5.2 The tests should had been conducted throughout the period of gestation, in successive generations of animals and dose escalation, the smallest of which must be approximately equivalent to human doses.

5.3 Please state the number of animals used in each group and it must be big enough to allow appropriate statistical evaluation.

5.4 Medicine studies evidence-based conducted and published in the last five years in internationally recognized scientific journals.

5.5 If deemed necessary, it would be required other related works about the effects caused by the drug.

CHAPTER III

PROCEDURE FOR OBTAINING THE HEALTH REGISTRATION

Medicines in general

Art. 11. To accept and process a registration request, it will be verified that the control form of the documentation is entered, is completed and signed by the applicant, that the number of documents that are declared are being delivered, and the magnetic file of

scanned documents. Should it fail any of the requirements or if the requesting form or the control form is not complete, the request will not be accepted for processing.

Art. 12. Upon reception of the application to request the health registration with its attachments, it shall be analyzed, starting with the technical documentary analysis, for which the INH has the maximum term of 30 days from the date of reception of the request, if there are observations at this time shall be notified once to the applicant. The notification should be picked up from the offices of INH, by applicant or whoever has a written authorization and the receipt of submission, despite of the fact that the INH will report it through an electronic monitoring system.

Art. 13. The applicant shall have a period of sixty (60) days from the date of receipt of the notification, to overcome objections to the application and its annexes. If within the period specified did not or does not comply with the request, the INH, within a period of ten (10) counted from the date of submission of the amendments or the expiry of the term specified, as appropriate, shall declare the application abandoned by a resolution and notify the applicant to withdraw the documentation within fifteen days after the notification of this administrative act. If the applicant does not withdraw the documentation, it will be destroyed.

In the event of declaring the application abandoned, the amount payed for the health registration won't be returned.

Art. 14. If the application and the attachments meet all specifications in the preceding articles, and the technical analysis report of the documents is favorable, the health registration shall be granted in the term up to 15 days, as provided under Article 4 of this regulation and 7 of the Regulation to the Organic Law of Health.

Art. 15. During the process for the health registration it will be determined the marketing status of the medicine, that is, if over the counter, by prescription of restricted circulation, with special recipe, or any other form determined by the health authority.

The evaluation of safety and efficacy of the products will be determined by the Pharmacological of the Health Registration area of INH whose functions and powers are established in the regulations to be issued for the operation of this committee.

New drugs

Art. 16. In the case of new drugs, scientific and technical laboratory tests needs to be made mandatory prior to marketing the product in the country, which will start if the application and the attachments meet all the requirements of the preceding articles and has a favorable technical analysis report for the documentation. The technical and scientific analysis will be made in the maximum term of one hundred and twenty days since this procedure starts. This scientific and technical laboratory analysis includes the safety and efficacy report, which must be prepared by the pharmacological committee of the health registration area of the INH that conforms to the case according to the specific regulations issued by the national health authority.

To make the scientific and technical laboratory analysis, the applicant shall submit to the National Institute of Hygiene the number of samples specified in the chart prepared for this purpose, which must have the expiration date not lesser than six months.

In the event that scientific and technical objections were found, the term shall be interrupted as appropriate.

Art. 17. If the technical and scientific laboratory analysis produces objections, they shall be notified to applicant, granting a term of one hundred twenty (120) days to overcome them. Once submitted all supporting evidence and overcame the objections of the case, it will continue with the analysis and the term will be reactivated.

Art. 18. The applicant may submit supporting evidence in order to overcome at once the technical and scientific objections, covering corresponding to the amount by way of value analysis quality control that has motivated, if it be the case.

If the objections have not been overcome, it will be issued a resolution denying the health registry, which will be notified to the applicant as stated in the preceding articles.

In the event that the health registration is denied, the amount payed for the health registration won't be refunded.

Once finalized all the procedures outlined in this article, if the applicant claims about results of the analysis, a new evaluation will be conducted with the samples (against samples), and must pay for the analysis.

Art. 19. Once finalized the above requirements and with favorable technical and scientific reports, in the maximum term of 15 days, it will be granted the health registration.

CHAPTER...

HEALTH DRUG REGISTRATION FOR HOMOLOGATION

Note: Chapter with its Articles added by Ministerial Agreement No. 710 published in the Official Gazette 542 of September 26th, 2011.

Note: Chapter amended by Ministerial Agreement No. 968, published in Official Gazette 586 of November 29th 2011.

Note: Ministerial Agreement No. 710 and Ministerial Agreement No. 968, repealed by Ministerial Agreement No. 1090, published in Official Gazette 729 of June 21st, 2012.

Note: Chapter and its Articles replaced by Ministerial Agreement No. 1090 published in Official Gazette 729 of June 21st, 2012.

Note: Ministerial Agreement No. 1090, repealed by Ministerial Agreement No. 2883, published in

Official Gazette 889 of February 8th, 2013.

Note: Chapter and its Articles replaced by Ministerial Agreement No. 2883 published in Official Gazette No. 889 of February 8th, 2013.

Art. ...- The National Health Authority, through the National Agency for Regulation, Control and Health Surveillance -ARCSA, or the agency performing its functions, shall grant the Health Registration Certificate for medicines for human use and consumption, imported by homologation.

Note: Article replaced by Ministerial Agreement No. 2883, published in Official Gazette 889 of February 8th 2013.

Art. ...- For Health Registration of Drugs in General, it would be understood as homologation the official acknowledgement of the Health Registration issued by Health authorities of the countries whose drug regulatory agencies have been qualified by the Pan American Health Organization (PAHO) / World Health Organization (WHO) as Regional

Reference Authorities, as well as those Health Registrations issued by the Health authorities of the United States, Canada, Australia, Japan, by the European Agency of Medicines (EMA) and the Ministry of Food and Drug Safety of the Republic of Korea.

Note: Article replaced by Ministerial Agreement No. 2883, published in Official Gazette 889 of February 8th 2013.

Note: Article replaced by Ministerial Agreement No. 4711, published in Official Gazette 204 of March 15th 2014.

Art ...- Regulatory approval was given for approval, all drugs have registered by the countries mentioned in the previous article; and biological drugs (Among them: vaccines, blood products, biotechnological and biosimilar), where they have been recorded by: these countries, provided they have specific regulations for the purpose.

The countries mentioned in the preceding articles shall be included in the list of countries validated by the National Health Authority and the National Agency for Regulation and Control Health-ARCSA, surveillance or acting skills, a body that will keep this list regularly updated and published through its website.

Note: Article replaced by Ministerial Agreement No. 2883, published in Official Gazette 889 of 8 February 2013.

REQUIREMENTS FOR DRUG HEALTH REGISTRATION BY HOMOLOGATION

Art ...- To obtain the Health Registration by homologation, it shall be submitted to the National Agency for Regulation, Control and Health Surveillance-ARCSA, or the agency doing its duties, the following documents:

a) Application Form, which must contain the information set out in Art. 5 of this Substitute Regulation of Sanitary Registration for drugs in general;

b) Notarized copy of the valid appointment of the legal representative or power of attorney registered in the Mercantile Register and copy of the RUC (Tax Registration Number), in case of legal persons; and, for individuals, a copy of identity or citizenship card and the RUC, if he had not submitted previous processes;

c) Duly authenticated authorization from of the product holder to request the Health Registration by Homologation;

d) Notarized copy of Health Registration Certificate issued by any country mentioned above;

e) Receipt of payment for the amount of Health Registration, according to valid regulations;

f) Notarized copy of the "Certificate of Pharmaceutical Product currently traded internationally" according to the WHO model or the" Free Sale Certificate " (counter drug) issued by the competent authority of health of the country of origin of the product, stating: product name, concentration and dosage form of the drug, complete quantitative and qualitative formula, name, city and country of the manufacturer;

g) A copy of the draft of internal and external tags that will be used for marketing in the country, written in Spanish, in clearly legible and indelible characters pursuant to the provisions of Article 31 of this Regulation.; and,

h) The prospect led the user, written in Castilian language with characters clearly legible and indelible, to be included in the medicine container.

The Biological drugs to get the Health Registration by Homologation, must also fulfill the requirements of the regulations, specific to them.

Note: Article replaced by Ministerial Agreement No. 2883, published in Official Gazette 889 of February 8th 2013.

PROCEDURE

Art. ...- The procedure for issuing the health registration of Medicines by homologation has the following steps:

1. The user must enter electronically automated system for granting the Health Registration Certificate, and once obtained their password, fill in the relevant application, and will enter the information required in the application form for registration of health registration Medicines for homologation.

2. The user must scan and enter into the system, all the documents described in Chapter Health Registration of Drugs by Homologation this Regulation.

3. The National Agency for Regulation, Control and Health Surveillance -ARCSA, or the agency performing its duties, in the term of one day, shall verify whether the documentation is complete and if the information entered in the application is correct.

4. If the documentation is not complete and correct, the system electronically shall notify the user, indicating the drawbacks found in the application. The user shall mend the application according to comments received and will have a term of eight (8) days for this activity, before it changes the status of the process. Should the user re-enter the application erroneously, or not enter before the deadline, the process will be canceled and the system will notify the reasons for the cancellation.

5. Once the documentation is complete and correct, payment of health registration is allowed. The system will notify the user the amount payable and the deadline for such payment, and the forms provided therefor.

6. Once the user makes the payment and is verified by the National Agency for Regulation, Control and Health Surveillance, and electronic invoice is created in the system and automatically sent to the user for printing.

7. After this process, the documents will be distributed to the departments responsible for the evaluation thereof, and within five (5) days the Health Registration Certificate shall be issued.

8. The Health Registration Certificate will be published in the system and available for the user to have access to it.

9. The user will enter the system with his/her password, select and print the Certificate of Health Registration.

10. Once issued the Health Registration Certificate by Homologation, the file with all he documentation will be sent automatically to the unit responsible for carrying out post-registration checks of medicines, to be included in its planning, in order to make the said control.

Note: Article replaced by Ministerial Agreement No. 2883, published in Official Gazette 889 of 8

February 2013.

Art. ...- For those drugs from countries whose stability studies have not been made for weather conditions of Zone IV (as classified by ICH for studies stability), the shelf life of the drug approval is six (6) months.

To extend the shelf life of the drug, the manufacturer must submit three stability studies under experimental conditions of humidity and temperature, for Zone IV weather (ICH Guidelines) or Pharmacopoeia of the United States of America, with duration equal to the proposed shelf life period.

Accelerated studies are accepted subject to the conditions and requirements set for zone IV by ICH Guideline, if applicable.

Note: Article replaced by Ministerial Agreement No. 2883, published in Official Gazette 889 of February 8yh 2013.

New Health Registration

Art. 20. It will be require a new health registration and must comply with the procedure pointed out in this regulation, when the following variations arise regarding the drug:

a) Change of concentration of the active ingredient;

b) New therapeutic indications;

c) Changes in chemical composition of the active ingredients;

d) Change of pharmaceutical form;

e) Change of manufacturing laboratory, the city or country;

f) Change in the composition formula to alter stability specifications and bioavailability of the product;

g) Change of the owner of the product; and,

h) New partnerships of active ingredients.

Art. 21. It is not necessary a new health registration or payment for it, in the following cases:

a) Changing the nature of the packaging material as long as the manufacturers submit:

1. Specifications of the new packaging material.

2. Certificate of analysis and stability sheets in the new packaging to prove: that the new package does not alter the stability of the product; and the qualitative and quantitative formula of the product has not been modified in relation to which was presented and approved in the previous health registration paperwork;

b) Change of product name;

c) Change of address of the manufacturer;

d) Change of company name of the holder of the product;

e) Change of name and address of the applicant;

f) Change the location of the manufacturing plant in the same city;

g) Change of distributor;

h) Change, increase or decrease of the presentation forms;

i) Change in size and / or color of the capsules;

j) Change, increase or decrease of excipients which do not affect the stability specifications or bioavailability of the product;

k) Changes in the shelf life of the product;

l) Inclusion of alternate manufacturer;

m) Change alternate manufacturer of the same city or country; and,

n) Elimination of alternate manufacturer.

The manufacturer or distributor shall communicate to INH, any of the modifications above-identified within thirty days after they happened.

Art. 22. The health registration won't be granted to the drug manufactured for the same holder of the product that has:

a) Same name and pharmaceutical form but different composition formula;

b) Same name, but pharmaceutical form and composition formulas are different, unless it is the same active ingredient that pharmaceutical art requires replace by its base or equivalent salt;

c) Different names and the same active ingredient(s), but the same and pharmaceutical form and composition, unless one of them is registered as generic; and,

d) A drugs from different manufacturers and / or owners, whose name is already registered in the Ecuadorian Health Registry.

Art. 23. When a pharmaceutical product that enters the health registration process with the category of new drug and for any reason does not end the process, this category will be transferred to the next pharmaceutical product that with the same active ingredient, association and / or route of administration requests a health registration.

Art. 24. When a new health registration is granted to a product with the same name generic name or brand because of manufacturer, city or country change, the previous health registration is automatically canceled.

Art. 25. The Ministry of Public Health in accordance with the provisions of Article 156 of the Organic Health Law will authorize the import of samples for purposes of health registration of drugs in the amounts set forth in the table prepared for this purpose subject to the regulatory codes.

They will be included in the import authorization, those active ingredients and excipients in the sufficient quantities set forth in the manufacturing techniques to produce a pilot batch for submission of samples required for sanitary registration of drugs of domestic manufacture.

Art. 26. For purposes of this regulation are considered as regulatory codes the set of rules and regulations contained in:

a) The Organic Health Law and its regulations;

b) The Pharmacopoeia of the United States of America; US National Formulary of North America; British Pharmacopoeia: International Pharmacopoeia; European Pharmacopoeia; French Codex, in that order of prevalence and its latest editions: and the Chinese Pharmacopoeia, as reference for processed natural products for medicinal use;

c) Regulations: General Code of Regulations of the Food and Drugs the E.U.A. (FDA), technical reports of the World Health Organization (WHO), guidelines of the International Committee on Harmonization (ICH) and others that the national health authority, consider necessary; and,

d) National Pharmacological Standards.

Reregistration Health Registry

Art. 27. The re-registration is the process by which the health registration certificate is updated, once its term has concluded, provided that the product retains all characteristics approved during registration. For this procedure the application should be submitted pursuant to the provisions of Art. 5 of this regulation, attaching the following documents, properly identified, foliated and signed both as hard copies and in digital:

a) A certified copy of valid operating license issued by the health authority competent;

b) Genuine and valid copy certificate of good manufacturing practices;

c) Original or notarized updated copy of certificate of pharmaceutical product traded internationally according to the WHO, or free sale certificate (over the counter drug), according to what is described in Article 7 of this regulation, issued by the health authority of the country of origin of the product (For imported drugs);

d) Original of previous health registration certificate;

e) Samples of the product in its original size with definitive labels, exactly as markets;

f) Four Original Tags. If the health authority requires any modification in this process, they may submit temporary tag as long as the holder or the product representative takes responsibility for the compliance of such modification;

g) Original Certificate of Analysis of the batch pending and long-term stability studies in experimental conditions of Climate Zone IV, in which is located Ecuador, with a duration

equal to the period of shelf life requested. If there were recent changes in the composition formula that require further studies of stability, may submit an accelerated study according to the conditions outlined in Article 6 literal n)numeral 2) including the modified qualitative and quantitative formula. These documents must include signature, Name and title of responsible pharmaceutical biochemical or pharmaceutical chemist;

h) Technical reports of at least two post-registration quality control analyses, made during the validity of previous health registration certificate, as established by the Organic Law of Health: and,

i) Proof of payment of the amount of the entitlement.

To the application and annexes it is necessary to attach a control form of the documents that are to be submitted for the registration process in the INI in which it should be identified with precision the documents attached as folio or folios; form which must be signed by the registrant, becoming the statement that the documentation is complete and meets all the requirements of this regulation.

Art. 28. Upon reception of the application and annexes for re-registration of the health registration, the institution shall proceed to technical analysis of documentation, for which the INH has a term of 15 days counted from the date of reception of the application; if they are observations at this time, those shall be notified the applicant once. The notification should be withdrawn, from the INH offices by the applicant or by a person authorized in written, despite of which, the INH will report to the electronic monitoring procedure.

Art. 29. The applicant shall have a term of fifteen (15) days from the date of reception of the notification, to overcome objections to the application and its annexes. If within the period specified did not overcome the objections, or did not observe the requested in them, the INH in a period of ten (10) days from the date of submission of the evidence to overcome objections or end of the term indicated, as appropriate, shall declare the application abandoned by resolution and notify the applicant to withdraw the documentation, within fifteen days of the notification of the administrative act. If the applicant does not draw back the documentation, it will proceed to destroy it.

In the event of declaring the application abandoned, the payment for the re-registration for the health registration, will not be refunded.

Art. 30. If the application and the attachments meet all specified in the preceding articles, and the report is favorable technical analysis of the documentation, the registration will be granted in the maximum term of fifteen (15) days, as provided under Article 4 of this Regulation and article 7 of the Organic Health Law.

CHAPTER IV

Labels and prospects

Art. 31. The external and internal labels must be written in Spanish and clearly legible and with indelible characters and must contain the following:

a) Name of product;

b) Generic name (INN);

c) The pharmaceutical form;

d) Net content of the container expressed in international system units, or the ones conventional of the activity when the previous ones were not available and number of units of the pharmaceutical form;

e) Quantitative and Qualitative formula. It has to be stated the percentage concentration of the active ingredient per dosage unit if applicable, with the generic name.- where the product requires the concentration of the active ingredients be declared in biological units with equivalence in weight units if possible.- For antibiotics equivalence in relation to its base. Abbreviations or acronyms shouldn't be used for chemic formulas. Internal labels must state the name and concentration of active ingredient;

f) Routes of administration may be excluded from the internal label with the exception of liquids for injection, ovules and vaginal tablets;

g) The number or batch code;

h) Unique code of the drug;

i) Pediatric use if the product requires it;

j) Storage temperature;

k) Laboratory manufacturer name, city and country of the same, if it operates under license control or other ways to determine the responsibilities of production, control and marketing.

In case of products packaged by a different firm than the manufacturer must declare the name of each, indicating its condition of participation. In the internal label it is accepted the manufacturer logo and can be omitted the name of the city;

l) Name responsible chemical pharmacist or biochemical pharmacist of the laboratory holder of the product (can be excluded in internal label);

m) Manufacturing and expiry date clearly legible and identifiable. It may be omitted the elaboration on the inside label, but the expiration date is mandatory;

n) Number of health registration or re-registration. On this last case the number of registration remains and it is followed by a digit indicating the number of times it has been re-registered;

o) Specification: counter, by prescription, under controlled prescription, of restricted circulation (can be excluded in the internal label);

p) To counter drugs, the label shall also state:

- Indications and instructions for use.

- Posology.

- Precautions.

- Warning: "If symptoms persist, consult your doctor."

- Contraindications; and,

q) In the case of medical samples, internal and external labels must also include the legend "Medical Sample, Not for Sale.

Art. ...- In the case of a generic drug, it is mandatory that on the external label appears in legible and indelible characters the word "GENERIC DRUG" with capital letters, in red, code, Red Pantone 032 and with a larger size than 20% compared the product name.

Note: Article added by Ministerial Agreement No. 2883, published in Official Gazette 889 of 8th February 2013.

Art. 32. If the primary packaging for its size does not allow the label to include all data required in the previous article shall contain: product name, logo or laboratory name responsible and lot number or code, or the concentration of active ingredients, date of expiration and health registration approval number. For injections also initial characters of the route of administration and the container contents. For vaginal ovules and tablets add the route of administration.

Art. 33. The labels, containers and prospects of new drugs that have not fulfilled the minimum requirements of the pharmacological tests or should include the following:

1. In the event that the submitted studies are incomplete, the warning: "This product should not be administered during pregnancy or when suspected its existence."

2. In cases where the parties have not submitted any of the required Teratology work, warning: "contraindicated in pregnancy or when suspected its existence."

3. If the product turned out to be teratogenic to some species of animals used in the studies, the warning: "contraindicated in pregnancy or when it suspected its existence.

Art. 34. When applying for enrollment for the health registration of a product, the applicant shall submit the project tags. Once approved health registration within a maximum period of ninety days submit the final labels with the number of health registration, essential requirement for marketing the drug.

Art. 35. In the packaging of all medicinal products should be included a prospectus intended for the user, which shall be consistent with the international pharmacological standards and existing scientific reports. The text of the prospectus will be submitted for approval as part of the documentation for the health registration and must include the following condensed basic updated information of product:

a) Identification of the product and necessary warnings to consult a doctor for any additional concern;

b) Active ingredients expressed qualitatively and quantitatively, list of excipients expressed qualitatively;

c) Pharmaceutical form and contents;

d) Name and address of the manufacturer and / or distributor;

e) Pharmaceutic-therapeutic group or type of activity in terms easily understandable to the patient;

f) The therapeutic indications;

g) Information necessary before taking the product, contraindications, precautions for use, interactions, special warnings (eg, pregnancy, pediatrics, geriatrics, precaution drive and operate machinery);

h) Instructions for appropriate use, with emphasis on the dosage, method and frequency of the administration and need to complete the treatment, action to take in case of dosage etc .; limitations of use; and in the case of time-counter medications;

i) Undesirable effects that may occur under normal use and, if necessary, actions that should be taken; and,

j) Storage conditions and the phrase "all medication must be kept out of reach of children".

CHAPTER V

Post registration Control

Art. 36. The national health authority shall perform periodically post-registration controls of the drugs that have obtained the certificate of health registration, by implementing monitoring and control actions in the place of manufacture, storage, transport and sale, Post-registration analyzes of quality control through samples of these products, which are subject to payment set by the national health authority, which must be paid by the holder of the health registration.

Art. 37. Sampling for post-registration quality control analysis will be carried out by professional pharmacists of the Provincial Directorates of Health and the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Perez (INH), which will act according to procedure established for this purpose and with the guarantees laid down in Article 258 of the Organic Law of Health; sampling is performed randomly

according to the technical standards issued for this purpose by the national health authority in: pharmaceutical laboratories, representation houses, pharmaceutical distributors, health services warehouses, local customs and other establishments approved for storage of medicines. The drugs sampled shall be within the period of their shelf life, in their original containers and with no alterations.

Art. 38. The representative samples taken from the same batch shall be divided into three numbered groups from one to three, conveniently packaged, labeled and sealed, of which on group will be given to the representative of the establishment that is performing the sampling, the other two will enter the INH, one to be delivered to the analytical laboratory for its technical and scientific analysis, the other as a counter sample for settlement cases.

Art. 39. If during the sampling it is found that the drugs do not meet the requirements established by law and / or technical specifications described in the corresponding health register, the INH automatically shall cancel the health registration certificate, until issued the results of quality control analysis and objections get overcame, for which, in the time frame of 48 hours, it shall be notified to the INH and will issue the corresponding resolution within 24 hours after the notification, without prejudice to any other penalties provided for law.

Art. 40. The analytical methodology for post-registration quality control analysis will be the same presented for obtaining health registration.

Art. 41. From the sampling study it will issued a minute in counterparts, which will be signed by the representative or owner of the establishment in which sampling is performed and professionals technicians who perform this activity, which shall contain among other data the amount of samples; A copy of the minute shall be submitted with the samples to the quality control laboratory of INH. Another copy shall remain on site, and the third copy shall remain on file at by the Provincial Directorate of Health to latter notify the holder of the health registration about the communication.

Art. 42. The costs of quality control analysis will be covered by the registrant, through the banking system, in the account assigned for the effect, under the name of the INH, in the term of 72 hours from the reception of the notification that the sampling of the drug(s) has been done, if the payment is not made, the analysis and the health registration shall be cancelled.

Art. 43. All medication must undergo quality control, at least twice, by random sampling during the term of the health registration, with samples shall be taken in any pharmaceutical establishment of the country, public or private.

Art. 44. For post-registration quality control of the drugs INH shall organize a completely independent process from the one contracted for the quality control analysis to grant the heath registration in the cases specified in this regulation.

Art. 45. It is an important component of the post-registration drug control the GMP inspections, the coordination of the program of good manufacturing practices for pharmaceutical laboratories is the responsibility of the Directorate General of Health through the Department of Control and Improvement of Health Surveillance.

GMP inspections will be carried out jointly with qualified technical staff of the Control and Improvement in Health Surveillance and the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Perez (INH), following the provisions of the appropriate regulations.

Art. 46. The national health authority, through its relevant technical units will conduct inspections to storage, distribution, import, export and marketing facilities, in order to verify compliance with good practices activities carried out in each of them, regardless of GMP inspections.

Art. 47. If the quality control results determine that the drug does not meet the standards under which the health registration was granted, the INH shall immediately notify the Department of Health Surveillance and Control to cancel the commercialization of the drug nationwide; also the INH shall suspend or cancel the health registration, as appropriate, as safety measure, until it is proven that the drug meets the quality standards.

Art. 48. The national health authority as part of the post-registration monitoring programs shall develop pharmacovigilance and drug utilization studies, in order to safeguard the safety of use thereof.

CHAPTER VI

Suspension or cancellation of health registration

Art. 49. The suspension or cancellation of health registration will be performed when it is proved that the drug or manufacturer doesn't meet the requirements and conditions set forth in the law and its regulations.

Art. 50. If it is detected that the drug would be likely to harm the health or if there are sanitary / health warnings related to safety and efficacy, the health registration will be canceled.

Art. 51. The Health registration will also be suspended or canceled, if as a result of monitoring and control actions is suspended, canceled or is not renewed the GMP certificate or operation license of the pharmaceutical establishment.

CHAPTER VI

Definition

Art. 52. For purposes of this Regulation the following definitions shall apply:

Unique Drug Code.- It is the code by which a drug is identified as it is marketed in the country, to facilitate the traceability of information thereof, it is composed by an alpha numeric number that identifies the active ingredient, its pharmacological action, pharmaceutical form and concentration among others.

Post registration control.- It is the set of technical and health activities to be undertaken in all stages from production to the use of the drugs, verifying that the establishments that produce, store, distribute, import, export, trade and expend meet technical and legal requirements of the current legislation, with the mission to safeguard quality conditions and safety of the drugs for human use as consumption, based on the standards under which the Health Authority granted the Health Registration.

Pharmaceutical Specialty.- It is the drug produced by a manufacturer under a special name or in a way that is characteristic.

Label.- It is any written or graphic expression that adheres or is printed on both the internal or primary, and externally or secondary packaging or container that identifies or

characterizes the medicine. It does not refer to the stickers on top of the label which are prohibited.

Manufacturer (Main).- Is the one that produces or manufactures the product.

Alternate Manufacturer: It is the additional manufacturer other than the main manufacturer, which manufactures for the same product owner, which is included in the health registration certificate.

Technical and scientific report.- They are the results of the examination of the technical and pharmacological documentation submitted by an applicant for the health registration, as well as the results of the quality control analysis of the drug subject to health registration.

Medicine / Drug.- It is all preparation or pharmaceutical form which composition formula expressed in units of the international system is constituted of a substance or mixture of substances, with constant weight, volume and percentages, manufactured in a pharmaceutical laboratory legally stablished, packaged and labeled to be sold as effective to diagnose, treat, alleviate, prophylaxis of a disease, physical anomaly or symptom, or for regaining, correction or modification of the balance of organic function of men and animals.

By extension this definition applies to the combination of substances of nutritional value, with therapeutic indications or specially prepared foods, to replace special food regimes.

Generic Medicine/Drug.- It is the one that is registered and marketed under the international non-proprietary name (INN) of the active ingredient, proposed by the World Health Organization; or, in absence of it, with a conventional generic name internationally recognized. These Medications must maintain standards of quality, safety and efficacy required for branded products.

New drug.- For purposes of obtaining health registration, it shall be construed as new medicine one whose active ingredient enters the country for the first time. It is including new partnerships, new indications, new routes of administration and / or dosage or concentration changes out the usual ranges of the active ingredient.

Nacional manufactured drugs.- They are the medicines that are manufactures and prepared and packaged in a national pharmaceutical plant.

Counter drug.- It is oral or topical medication that because of its composition and action of their pharmacological active ingredients, is authorized to be expended or distributed without prescription.

Imported drugs.- They are drugs made outside the territory of Ecuador, that have entered the country as imports.

Original sample.- For purposes of obtaining health registration, it is the form of presentation declared, which is as it is marketed in the country of origin.

Prospectus.- It is the prospectus (information sheet) for the user included as part of the medicine.

Country of origin.- Is the country from which the drug is imported to Ecuador, whether it is subject to go through a distribution central.

Biologic products.- They are serums, vaccines, toxins, antitoxins, hormones, vitamins, antibiotics, enzymes and the ones that are so declared, the preparation of which is obtained from bacteria, fungi, animal organs or active ingredients produced, isolated or semi-synthetized therefrom. They are also the genetically engineered.

Health Registration.- It is the certification issued by the national health authority for importing, exporting and marketing of products for use and human consumption listed in Article 137 of the Organic Law of Health. Such certification is granted when the product meets the requirements of quality, safety, efficiency and ability to consume and use such products fulfilling the paperwork procedures established under the Law and its Regulations.

Health risk.- It is defined as the probability of occurrence of an exogenous adverse event, known or potential to endanger human life or health, arising from population exposure in biological, physical, chemical factors, production, marketing, distribution, use, consumption or possession, among others, of the product.

Applicant.- It is the natural or legal person applying for drug health registration. It could be the manufacturer, proxy or authorized distributor.

Health Registration.- It is the natural or legal person to whom the certificate is issued for licensing, and is the legal and technically responsible for the product quality in the country.

Holder or the Product.- It is the natural or legal person owning the product, which should be demonstrated by documentation.

GENERAL PROVISIONS

FIRST: The breach of the provisions of this regulation will result in the application of the penalties established in the Organic Law of Health in this legal instrument.

SECOND: The technical and administrative procedures for granting of marketing authorization, re-registration and post-registration analyzes of quality control should be performed in accordance with established procedures manuals of each area developed for that purpose by the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Perez (INH) for approval and formalization of the Minister / or public health.

THIRD: It is repealed the Regulation of Health Registration for Drugs in General, issued in the Ministerial Agreement No. 00000236 published in Official Gazette No. 188 May 7th 2010, and any other provision of equal or lower rank that oppose it.

FOURTH: Applicants or holders of Health Drug Registration for approval must have in their establishments duly authorized by the Nacional Health Authority, the following documentation:

a) Chemical, physico-chemical and microbiological specifications of the finished product, original document with name, signature and title of responsible pharmaceutical chemist or pharmaceutical biochemical; and,

b) Analytical methodology necessary for analysis of post-registration effect and quality control of the product, as defined in Article 40 of this Regulation.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

Fifth: Applicants or holders of Health Registration of the Drug by homologation, must have in their establishments duly authorized by the National Health Authority, the Protocol of

three (3) sheets of chemical and microbiological stability of the drug, pointing out the humidity and temperature corresponding Climate Zone IV, with original signature, name and title of technical manager of the study, to ensure the useful shelf life assigned. For products requiring refrigeration or freezing, determine the temperature corresponding with the relevant stability studies.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

Sixth: The documentation described in the Fourth and Fifth General Provisions shall be requested by the National Agency for Regulation, Control and Health Surveillance -ARCSA, or the agency performing its duties at the time that this institution requires.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

TRANSITORY DISPOSITIONS

FIRST.- Within one hundred twenty days from the date of execution of this regulation, the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Perez (INH) will prepare, for approval of the Minister of Public Health, technical procedures manuals and administrative procedures for granting health registration, re-registration and Post-registration quality control, which will be updated and formalized to the extent that circumstances required, as well as the single format for the health registration certificate.

SECOND.- In the term of 180 days from the date of execution of this regulations, INH, shall reorganize its units for application of the provisions of this legal instrument.

THREE.- From the date of execution of this regulation, the INH has a term of ninety days to issue resolutions for abandonment of proceedings in all cases where that stakeholders have not overcame the objections.

FOURTH.- It is suspended reception of new applications for enrollment in the health medication for 60 days, counted from the date of signature of this regulation.

FIFTH.- The requirement for bioequivalence established in Article 6, paragraph t) of this regulation, in the case of locally manufactured medicines, will be implemented gradually, according to the technical standards developed within 120 days from the date of signature

of this regulation, by the National Institute of Hygiene and Tropical Medicine Dr. Leopoldo Izquieta Perez for approval and formalization of Minister of Public Health.

SIXTH: For the implementation of Art. 3 of this Ministerial Agreement, it is granted a term of three hundred and sixty (360) days from the signing of it.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

SEVENTH: Within thirty (30) days from the execution of this Ministerial Agreement, the National Agency for Regulation, Control and Health Surveillance -ARCSA, or the agency performing its duties, shall develop the necessary instructions for the implementation of the approval of Health Registry of Drug, in accordance with the provisions of this reform.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

EIGHTH.- For the paperwork to get approval for health registration by homologation, of a drugs coming from countries that are previously determined and that have submitted the application until the date of execution of this Ministerial Agreement, the National Agency for Regulation, Control and Health Surveillance –ARCSA, or the agency performing its duties, shall make a schedule giving priority to such procedures, until regularize requests that are pending, according to the Instruction to be issued for the purpose.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

NINE.- Until the National Agency for Regulation, Control and Health Surveillance -ARCSA, or who exercises its powers, completes its process of implementing the computer system, technical and legal requirements of this Regulation, for obtaining Health Registration of the Drug by homologation, will be physically entered by users in a folder duly paginated and signed by the technician, enclosing a copy of those scanned documents on a CD. Likewise the documentation to overcome objections will be received and reports will be given at the National Agency for Regulation, Control and Health Surveillance -ARCSA.

Note: Provision added by Ministerial Agreement No. 2883, published in Official Gazette 889 February 8th 2013.

Art. Final.- This Regulation shall been force since its execution, regardless its publication in the Official Gazette. For the performance of this Regulation are responsible the General Directorate of Health, the Control and Improvement on Health Vigilance Directorate the National Institute of Hygiene and Tropical Medicine and Dr. Leopoldo Izquieta Perez.

Executed in the Metropolitan District of Quito, October 27th, 2010

f.) Dr. David Chiriboga Allnutt, Minister of Public Health.

It is a true copy of the document contained in the file of the Legal Counsel Department, which I refer if necessary, I certify.- Quito, October 28th, 2010. f.) Dra. Nelly Cecilia Orquera Mendoza, General Secretary, Ministry of Public Health.

NOTE: "This is a translation form the original version in Spanish. This translation is for information purposes only. All legal and/or binding documents shall be interpreted form the official version only, which is the original Spanish version".