**ANNEX OF RESOLUTION No. 303-2013 (COMIECO-EX)**

**CENTRAL AMERICA RTCA 11.03.64:11**

**TECHNICAL**

**REGULATION**

**PHARMACEUTICAL PRODUCTS**

**NATURAL MEDICINAL PRODUCTS FOR HUMAN USE**

**REGISTRATION REQUIREMENTS**

**CORRESPONDENCE**: This regulation does not correspond with any documents.

ICS 11.120.10 RTCA 11.03.64:11

Central American Technical Regulation, edited by:

* Ministry of Economy, MINECO
* Salvadoran Agency for Technical Regulation, OSARTEC
* Ministry of Development, Industry and Commerce, MIFIC
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**REPORT**

The respective Technical Committees for Technical Regulations across the Entities Technical Regulation of Member states of the Central Region, and their successors, are the bodies responsible for carrying out the study or the adoption of the Technical Regulations. They are composed of representatives of the Government, Consumer Protection Organizations, Academic and Private Sector.

This document was approved as Central American Technical Regulations RTCA11.03.64:11 PHARMACEUTICAL PRODUCTS. NATURAL MEDICINAL PRODUCTS FOR HUMAN USE. HEALTH REGISTRATION REQUIREMENTS, by the Subgroups on Standardisation Measures and Medicines and Related Products from the Central American Region. The formalisation of this Technical Regulation implies the adoption by the Council of Ministers for Economic Integration (COMIECO).

**PARTICIPATING MEMBERS OF THE COMMITTEE**

**For Guatemala**

Ministry of Public Health and Social Welfare

**For El Salvador**

National Directorate of Medication

**For Nicaragua**

Ministry of Health

**For Honduras**

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**For Costa Rica**

Ministry of Health

1. **OBJECTIVE**

To establish the conditions and requirements under which the health registration of natural medicinal products for human use for marketing is granted.

1. **SCOPE**

It applies to natural medicinal products for human use that is manufactured or imported, natural or legal persons for marketing in the Member States of the Central American region.

This excludes those products that are added to active substances of chemical synthesis or isolated from natural material responsible for pharmacological activity, as well as dosage forms that are applied via parenteral and ophthalmic administration.

1. **DOCUMENTS TO CONSULT**
   1. RTCA Pharmaceutical Products. Natural Medicinal Products for Human Use. Labelling requirements. In force.
   2. RTCA Pharmaceutical Products. Natural Medicinal Products for Human Use. Quality Verification. In force.
2. **Definitions and terminology**
   1. **Competent authority:** authority responsible for the issuance of the certificate of free sale and certificate of good manufacturing practices for natural medicinal products in each country or region.
   2. **Regulatory authority**: authority responsible for the health regulations in each country or region.
   3. **Good Manufacturing Practices**: A set of procedures and rules designed to ensure the uniform production of batches of natural medicinal products that meet quality standards.
   4. **Certificate of Good Manufacturing Practices**: document issued by the competent authority of the country in which the manufacturer laboratory is located, where it is certified that the laboratory complies with good manufacturing practices.
   5. **Free Sale Certificate**: document issued by the competent authority of the country of origin or provenance, which certifies that the natural medicinal product, has its current registration and is authorized for sale or distribution in that country.
   6. **Registration certificate**: official document issued by the competent authority authorising the marketing of a natural medicinal product.
   7. **Committee of experts**: Group of people who, by their suitability, is recognised by the regulatory authority, to endorse the documents that support the use and safety of a natural active substance or of a natural medicinal product.
   8. **Contract manufacturing**: legal document concluded between the owner of the natural medicinal product and manufacturer which establishes the conditions, commitments and other circumstances for the manufacture of one or more products.
   9. **Natural drug**: naturally occurring substance and activity used alone or combined in the development of natural medicinal products.
   10. **Packaging or container**: all material used to protect in handling, storage and transportation of the natural medical product.
   11. **Primary packaging or container**: container into which the natural medicinal product is placed directly in the finished form.
   12. **Secondary packaging or container**: final container of distribution and marketing or packaging into which the primary container is placed that contains the natural medicinal product in final pharmaceutical form.
   13. **Specific epithet**: Latinised name that accompanies the genus, to form the binomial name of a species.
   14. **Stability studies**: tests performed to determine the period of validity of the natural medicinal product in its original primary packaging and storage conditions specified.
   15. **Labelling**: compulsory information on the tag, label, image or other graphic or descriptive matter, written, printed, stencilled or marked in relief, which is attached or included in the packaging of a natural medicinal product.
   16. **Excipient**: substance without pharmacological action to the concentration used, which determines or modifies the consistency, form, volume or physicochemical properties of the preparations of natural medicinal products.
   17. **Extract**: preparations of liquid consistency (fluid extracts and tinctures), semisolid (soft extracts) or solid (dry extracts) obtained from natural drugs.
   18. **Standardised Extract**: extract that provides a minimum level or specific range of one or more constituents, whether or not with pharmacological activity, as long as it maintains the identity of the natural drug where it comes from.
   19. **Third party manufacturing**: national or foreign manufacturing made within the limits of a previous contract between the owner of the medicinal natural product and the manufacturer.
   20. **Expiration date or maturity date**: date established for each batch placed on the primary and secondary packaging until which it is expected that the natural medicinal product, stored properly meets quality specifications.
   21. **Methods of sales**: variants of natural medicinal products which can be marketed, being the following:
       1. Medical prescription product;
       2. Over-the-counter product.
   22. **Monograph of finished product**: technical scientific description of the safety profile and effectiveness, according to the evidence level of a natural medicinal product.
   23. **Scientific name**: binary name of the species, genus and specific epithet.
   24. **Country of Origin**: country where the product is manufactured. In case intervene in manufacturing laboratory more than one manufacturer, the country of origin is that in which the manufacture of at least the bulk product is made.
   25. **Country of Departure**: country from which the product is distributed, conditioned or exported. Whenever these are involved in the manufacturing process; at least until the primary package.
   26. **Natural preparation**: obtained from natural raw material by process fractionation, extraction with solvents, expression, distillation, purification, fermentation, concentration or any other physical or biological processes.
   27. **Natural medicinal product**: processed product, industrialised and labelled with medicinal properties, which contains in its formulation ingredients obtained from plants, animals, minerals or mixtures thereof. It may contain excipients in addition to the natural material. Natural medicinal products that are added to active substances of chemical synthesis or isolated from natural material responsible for pharmacological activity are not regarded as medicinal natural products.
   28. **Traditional natural medicinal product**: the one whose use and safety of the natural active substances is justified by ethno-medical reports, technical and scientific documentation, indexed publications or documents endorsed by a committee of experts. They are used for oral, topical or other routes that do not require sterility.
   29. **Responsible Professional**: professional pharmacist or pharmaceutical chemist, responsible for processing health registration to the regulatory authority, authorized by the owner of the product or its legal representative through a power granted according to the laws of each State party.
   30. **Health Registration**: procedure of approval by the competent authority of a country for the marketing of a natural medicinal product, once it has passed the evaluation process concerning the quality, efficacy and safety.
   31. **Legal Representative**: natural or legal person residing in the country where registration is processed, authorised by the owner of the natural medicinal product, through a power granted according to the laws of each State party, that can respond to the regulatory authority.

NOTE: For the case of El Salvador the figure of the legal representative or agent may be used.

* 1. **Natural active substance**: chemically defined substance or groups of substances, whose pharmacological action referred to and is responsible for therapeutic effects present in the natural medicinal product. When the chemical substances mentioned above are unknown, they are considered active substances of the natural drug or the natural preparation.
  2. **Product owner or owner of the registration**: natural person or legal owner of the product.
  3. **Traditional use**: is supported with documentary evidence that state that the natural drug that is used in a product, has been used for three or more decades for medicinal purposes.
  4. **Shelf life**: period during which it is expected that a product, if stored properly, will keep the established specifications.

1. **CATEGORIES OF ACCEPTANCE OF INGREDIENTS IN A NATURAL MEDICAL PRODUCT**
   1. **Ingredients accepted:**
      1. Natural drugs
      2. Natural preparations
      3. Combinations of any of the above
      4. Pharmaceutically accepted excipients
   2. **Ingredients not accepted:**
      1. Molecules isolated from natural ingredients and compounds of chemical synthesis or semi-synthesis used as an active ingredient, which by definition are excluded from natural medicinal products.
      2. Natural substances prohibited in accordance with international recommendations or regulations issued in each State Party.
      3. Species identified as protected or endangered unless they come from managed crops or breeding.
      4. Homeopathic ingredients (strains, mother tinctures and dilutions).
2. **PHARMACEUTICAL FORMS**

All pharmaceutical forms which demonstrate the safety and effectiveness are accepted, except those that are applied by ophthalmic and parenteral route.

1. **PROVISIONS FOR THE HEALTH REGISTRATION**
   1. For import, production, distribution, marketing, prescription, promotion and advertising, all natural medicinal product require prior sanitary registration with the regulatory authority.
   2. The health registration of natural medicinal products will be valid for five years, which may be suspended or cancelled when there are duly substantiated health reasons of a scientific, technical or legal character.
   3. Any official or legal document issued abroad must be legalised in compliance with the specific national regulations.
   4. Any official or legal document required for registration must be valid at the time of submission. Official documents shall be valid from the competent authority that grants them of the country where it is issued. In cases where the validity is not specified, this will be 2 years from the date of issue for purposes of the registration process.
   5. Any official or legal document must be submitted in original or certified copy pursuant to the laws of each State Party. The document must be presented in Spanish / Castilian language or if submitted in another language, it must be accompanied by respective translations issued in accordance with the laws of each State Party.
   6. No corrections to the certifications or the official documents presented are permitted, unless they are supported by the same body that issued the original document.
   7. In those cases that apply and for the purposes of registration of a specific natural medicinal product, the applicant will be allowed to refer to existing original documents stated in files of the regulatory authority. In this case the applicant should refer to the management in which the original document was delivered, presenting a photocopy of it.
   8. The administrative procedure for processing health registration, renewal and modifications, will be done according to the domestic law of each State Party.
   9. Noncompliance with this regulation “Pharmaceuticals. Natural Medicinal Products for Human Use. Health Registration requirements” will result in the application of the provisions of the sanctions regime of each State Party.
   10. This regulation “Pharmaceuticals. Natural Medicinal Products for Human Use. Health Registration requirements”, only repeals the provisions of the requirements for health registration, renewal and modification of natural medicinal products of the internal regulations of each State Party.
   11. Correspond to the same record:
       1. Different commercial presentations of medicines with the same concentration and the same pharmaceutical form.
       2. Medicines with the same qualitative and quantitative formula and different flavour and / or colour.
2. **REQUIREMENTS FOR HEALTH REGISTRATION**
   1. Proof of payment.
   2. Application for health registration signed and sealed by the responsible professional, containing information detailed in Annex 1.
   3. Powers that prove the legal and/or technical representation provided by the owner, by the natural or legal person(s) according to the legislation of each country (original or certified copy of the document).
   4. Certificate of free sale of the product, issued by the authority competent of the country of origin or departure.
   5. Certificate of Good Manufacturing Practice, from each of the establishments involved in the manufacture of the product, when this is not included in the certificate of free sale, stating the pharmaceutical form and type of product to register, issued by the competent authority of the country or countries where the manufacturing process is carried out, or equivalent document issued by the competent authority, document issued by the regulatory authority stating that it conducts periodic inspections of the establishment but does not extend the certificate of good manufacturing practices.
   6. Manufacturing contract or alternatively the relative excerpt of the portions of the manufacturing contract, when applicable, in original or authenticated or certified copy of the legalised document, that contains at least the following information:
      1. Signed by the owner and the manufacturer jointly or separately.
      2. Commitment to comply with good manufacturing practices.
      3. Establish the conditions of production, analysis, when applicable or any other technical management related to these.
      4. It should describe the handling of raw materials, packaging materials, bulk and finished product and in the case that they are rejected.
      5. Allow the registrant to the facilities of the contractor (contracted) for audits.
      6. Allow the entry of the contractor (contract) to the facilities of the registrant.
      7. List each of the products or services of analysis covered by the contract.
   7. Complete qualitative and quantitative formulation of the product per unit of dose. Must be submitted in original signed and stamped by the responsible professional of the manufacturer’s laboratory, indicating:
      1. Name(s) of the active substance(s):
         1. Scientific name of the organism from which drugs or natural preparations are obtained, indicating the part or organ used.
         2. Chemical name or internationally accepted name, for mineral drugs or their preparations.
      2. Solvent used, in liquid extracts. If the solvent is ethanol, the percentage must be declared.
      3. Drug/solvent or excipient relationship, in the case of extracts or the standardisation declared by the manufacturer of the extract.

NOTES:

* 1. All excipients of the product must be described with their name internationally accepted.
  2. The units of each component should be given according to the international system of measurement (SI).
     1. Qualitative composition of the empty capsules.
     2. Composition of the printing inks on the capsules, tablets and coated tablets.
     3. For topical dosage forms, the formulation must be in 1 g, 100 g, 1 mL or 100 mL.
  3. Monograph of the finished product.

The monograph, should correspond to the pharmaceutical form of the product to register, which must contain the following information:

* + 1. Name of the product.
    2. Composition:
       1. Scientific name of the organism from which drugs or natural preparations are obtained, indicating the organ used.
       2. Chemical name or internationally accepted name, for mineral drugs or their preparations.
    3. Pharmaceutical form.
    4. Preparation form.
    5. Drug information, which include:
       1. Instructions.
       2. Occasions when the product should not be used (e.g. pregnancy, diabetics).
       3. Precautions and warnings.
       4. Maximum time of use, when applicable.
       5. Interactions (“not to be taken with”).
       6. Adverse effects.
       7. Dosage and route of administration.
       8. Recommendation in case of overdose or abuse, when applicable.
       9. Bibliographic references.
       10. Date of revision of the monograph.
  1. Safety and efficacy information in accordance with Annex 3 to this Regulation.
  2. Analytical methodology.
  3. Specifications of the finished product.
  4. Labelling of primary or secondary packaging or container and insert (as applicable), in original or draft, according to regulations in force.
  5. Stability study report.

NOTE: Pending the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use” in force, shall be required.

* 1. A copy of the finished product, for pharmaceutical evaluation.
  2. Original samples of finished product, in accordance with the matching quantity to perform the analysis, according to the “RTCA Natural Medicinal Products for Human Use. Verification of Quality” in force.
  3. Standards or standardised raw material to perform the analysis, when required by the methodology of analysis.

NOTES:

1. Requirement 8.14 will not apply in the case of Guatemala as the test samples are used.
2. Requirements 8.15 and 8.16 will be requested after the registration of the natural medicinal product for the case of Costa Rica and El Salvador.
3. **REQUIREMENTS FOR THE RENEWAL OF HEALTH REGISTRATION**

The renewal of the health registration of a natural medicinal product can be managed at least three months before its expiration.

Once the health registration is expired it will not be possible to market the product, and it must be processed as a new record.

If during the 6 months following the expiration of the registration of the medicinal natural product, the interested party requests to keep the number assigned by presenting justified reason, the regulatory authority will keep the original number, however, during this period, it may not be marketed.

Renewal is not granted, having approved the changes after the requested registration.

* 1. When the product maintains the information and features that have been approved during the term of registration, the applicant for renewal must submit:
     1. Proof of payment of registration renewal.
     2. Application for renewal of health registration signed and sealed by the responsible professional containing the information detailed in Annex 1.
     3. Affidavit issued by the owner or his legal representative or by the professional responsible for the registration through power issued by the owner of the product, that the information and product features have not changed since the last request for amendment filed with the regulatory authority.
     4. Certificate of free sale of the product, issued by the competent authority of the country of origin or departure.
     5. Certificate of Good Manufacturing Practice, from each of the establishments involved in the manufacture of the product, when this is not included in the certificate of free sale, stating the pharmaceutical form and type of product to renew, issued by the competent authority of the country or countries where the manufacturing process is carried out, or equivalent document issued by the competent authority, document issued by the regulatory authority stating that it conducts periodic inspections of the establishment but does not extend the certificate of good manufacturing practices.
     6. Stability Study Report to confirm the approved shelf life.

NOTE: Pending the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use”, shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the shelf life period requested.

* 1. In the cases where the natural medicinal product presents modifications to the health registration that are not known to the Regulatory Authority, the modifications may be applied simultaneously with the renewal.

Similarly if the affidavit cannot be submitted, in both cases the following requirements must be met:

* + 1. Proof of payment.
    2. Application for renewal of health registration and modifications signed and sealed by the responsible professional containing the information detailed in Annex 1.
    3. Powers that accredit the legal and/or technical representation provided by the owner to the natural or legal person(s) according to the legislation of each country (original or certified copy of the document).
    4. Certificate of free sale of the product, issued by the authority competent of the country of origin or departure.
    5. Certificate of good manufacturing practices, as set out in paragraph 8.5 of registration requirements.
    6. Contract of manufacturing, where applicable, in accordance with paragraph 8.6 of registration requirements.
    7. Full qualitative and quantitative composition of the product per unit dose, in accordance with paragraph 8.7 registration requirements.
    8. Finished product specifications.
    9. Labelling of primary or secondary packaging or container and insert (as applicable), in original as is being marketed, according to labelling regulations in force.

NOTE: When the product has not been marketed, the draft artwork of the primary and secondary packaging in Spanish, accompanied by an affidavit of the owner of the product that indicates that the product has not been sold, will be accepted.

* + 1. Stability Study Report that confirms the shelf life.

NOTE: Pending the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use”, shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the shelf life period requested.

* + 1. Depending on the requested amendment the documents according to Annex 2 must be submitted.

1. **CAUSES OF NON-GRANTING OF THE HEALTH REGISTRATION.**

The health authorities of States Parties shall not issue the health registration of a product when:

* 1. It does not meet the requirements
  2. The formula contains ingredients reported as not safe or in doses and routes not allowed.
  3. The formula contains ingredients with therapeutic antagonistic effects.
  4. The therapeutic properties of the product cannot sustain itself.

1. **CAUSES OF CANCELLATION OF THE HEALTH REGISTRATION**

The health authorities of States Parties cancel the health registration of a product when:

* 1. It is found that the product proves to be harmful or unsafe in the normal conditions of use.
  2. For forgery or alteration of documents submitted to the regulatory authority.
  3. When it is established that the product does not have the authorised quantitative or qualitative composition or when it fails to comply with the guarantees of quality and stability declared in the dossier, following due process according to the laws of each State party.
  4. When requested by the owner of the product.
  5. It has been demonstrated with conclusive scientific evidence that the product has no therapeutic properties for which was initially registered.

1. **MODIFICATIONS TO THE HEALTH REGISTRATION**

Any change in the information that is made after the health registration, shall be as set out in Annex 2.

When there are changes in natural active ingredients, dosage form and strength of the product, a new record must be submitted.

1. **MONITORING AND VERIFICATION**

The monitoring and verification of this Technical Regulation corresponds to the regulatory authorities of the States parties of the Central American region.

**--END OF THE TECHNICAL REGULATION--**

**ANNEX 1**

**(Normative)**

**Application for the health registration, required information**

1. **Product data**
   1. Product name.
   2. Name of the natural active substances.
   3. Pharmaceutical form.
   4. Route of administration.
   5. Presentation of the product.
   6. Proposed shelf life.
   7. Method of sale.
   8. Registration category (new, renewal).
2. **Manufacturer and packer information** 
   1. Name and country of the laboratory/laboratories involved in the manufacturing.
   2. Address, telephone, fax and email.
   3. Stage of manufacture.
   4. Health license or health permit number of operation and expiration date (when it is national).
3. **Information on the owner of the product** 
   1. Name.
   2. Address, telephone, fax and email.
   3. Country.
4. **Information on the distributor/distributors**
   1. Name of the distributor/distributors.
   2. Address, telephone, fax and email.
   3. Health license number and expiration date.
5. **Information on the legal representative**
   1. Name.
   2. ID number.
   3. Address, telephone, fax and email.
6. **Information on the responsible professional**
   1. Name.
   2. ID number.
   3. Address, telephone, fax and email.
   4. Registration number or pharmaceutical chemist enrolment.
7. **Key that is considered a sworn statement in the application.**

**ANNEX 2**

**(Normative)**

**Requirements for modifications to the health registration**

1. Modifications that prior require approval from the Authority regulating.

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| **MODIFICATION** | **REQUIREMENTS** |
| 1. In the commercial presentation. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       4. Document issued by the owner or his legal representative that states the change. |
| 1. In the product name. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Document issued by the owner or his legal representative that states the change of name.       4. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force. |
| 1. Trade name of the manufacturer, packer or owner. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Legal document certifying the change.       4. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force. |
| 1. In the monograph and insert. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Monograph and insert updated with the requested changes.       4. Bibliographic reference or otherwise, studies as set out in the registration requirements that support the change.       5. Document issued by the owner or his legal representative that states the change. |
| 1. In the shelf life period. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Stability study report that confirms proposed shelf life.   NOTE: Until the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use”, shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the shelf life period requested.   * + - 1. Document issued by the owner or his legal representative that states the change. |
| 1. In the storage conditions. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Stability study report that supports the requested conditions.   NOTE: Until the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use” shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the conditions requested.   * + - 1. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       2. Document issued by the owner or his legal representative that states the change. |
| 1. Of the primary packer. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Certificate of good manufacturing practices of the new packer.       4. Contract with the new Packer, in case of manufacturing for third parties.       5. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       6. Affidavit expressing that the same conditions concerning the qualitative and quantitative formula, type and material of primary packaging, process and place of manufacturing of the registered product are maintained.       7. Document issued by the owner or his legal representative that states the change. |
| 1. Of the secondary packer. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Certificate of good manufacturing practices of the new packer.       4. Contract with the new Packer, in case of manufacturing for third parties.       5. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       6. Document issued by the owner or his legal representative that states the change. |
| 1. Type of primary packaging material or container closure system. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Stability study report.   NOTE: Until the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use” shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the new type of packaging material or container closure system.   * + - 1. Specifications of the primary package or container closure system.       2. Document issued by the owner or his legal representative that states the change. |
| 1. Addition of a new primary packaging | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Stability study report for the requested package.   NOTE: Until the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use” shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the new packaging.   * + - 1. New original labels for containers/packaging primary, secondary (when applicable) or drafts according to RTCA Labelling of Natural Medicinal Products in force.       2. Specifications of the primary package.       3. Document issued by the owner or his legal representative that states the change. |
| 1. Of the owner. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       4. Legal document certifying the change attaching the new powers.       5. Contract of accordance to the paragraph 8.6 in case of manufacturing for third parties. |
| 1. In case of manufacturing for third parties: 2. Change of manufacturer. 3. Change of manufacturer and country of origin. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Certificate of free sale of the product.       4. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       5. Certificate of good manufacturing practices of the new manufacturer.       6. Stability study report.   NOTE: Until the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use” shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the product manufactured at the new plant.   * + - 1. A copy of the finished product.       2. Samples of the finished product for analysis in accordance with the provisions of the RTCA Verification of Quality in force.   NOTE: In the case of Costa Rica and El Salvador the submission of samples does not apply, because it conducts analysis post-approval.   * + - 1. Analytical methodology.       2. Contract with the new manufacturer in accordance with paragraph 8.6.       3. Document issued by the owner or his legal representative that states the change. |
| 1. Method of sale. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Information justifying the change issued by the owner or his legal representative.       4. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force. |
| 1. Change of excipients or change in the concentration of the same. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Quali-quantitative formula per unit of dose       4. Stability study report.   NOTE: Until the entry into force of the RTCA of Stability Studies for Natural Medicinal Products, the analysis report of the physical, chemical and microbiological tests as set out in the “RTCA Verification Quality Natural Products for Medicinal Use” shall be required, demonstrating that the product is within the specifications presented in the registration dossier for the product manufactured for the new formulation.   * + - 1. Samples of finished product with its specifications, when applicable.   NOTE: In the case of Costa Rica and El Salvador the submission of samples does not apply, because it conducts analysis post-approval.   * + - 1. Technical justification for the change.       2. Analytical methodology of the finished product, when applicable.       3. Updated finished product specifications, when applicable.       4. Document issued by the owner or his legal representative that states the change. |
| 1. Information on the primary and secondary labeling | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. New original labels for containers/packaging primary, secondary or drafts according to RTCA Labelling of Natural Medicinal Products in force.       4. Technical justification for the change issued by the holder or his legal representative. |
| 1. Manufacturing site within the same country. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Certificate of good manufacturing practices.       4. Affidavit owner of the product or legal representative to the effect that manufacturing conditions have not changed.       5. Document issued by the owner or his legal representative that states the change. |
| 1. Legal representative or responsible professional. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Power granted according to the laws of each State Party attesting to the change. |

1. Changes to be notified to the Regulatory Authority and do not require prior approval.

|  |  |
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| **MODIFICATION** | **REQUIREMENTS** |
| 1. Material or dimensions of the secondary packaging. | * + - 1. Notification signed and stamped by the responsible professional.       2. Document issued by the owner or his legal representative that states the change.       3. Original packaging or drafts. |
| 1. Design of the labeling of the primary and secondary packaging. | * + - 1. Notification signed and stamped by the responsible professional.       2. Document issued by the owner or his legal representative that states the change.       3. Original packaging or drafts. |
| 1. Discontinuation of registered presentations. | * + - 1. Notification signed and stamped by the responsible professional.       2. Document issued by the owner or his legal representative that states the change. |
| 1. Change or extension of distributor. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Document issued by the owner or his legal representative that endorses the change or extension. |
| 1. Change in the product safety information. | * + - 1. Proof of payment.       2. Request signed and stamped by the responsible professional.       3. Document certifying the change.       4. Monograph and insert with the marked change when the product includes it. |

**ANNEX 3**

**(Normative)**

**CLASSIFICATION OF NATURAL ACTIVE SUBSTANCES BASED ON EFFECTIVENESS AND SAFETY**

1. **Levels of security**: on the basis of the general guidelines of Agency for Health Care Policy and Research of the United States (AHCPR), World Health Organisation (WHO) and the European Medicines Agency (EMA), active substances natural are classified according to their safety and efficacy as follows:

|  |  |  |
| --- | --- | --- |
| **Evidence Level** | **Type of Evidence** | **Grade** |
| **Ia** | Meta-analysis of randomised and controlled clinical trials | **A** |
| **Ib** | At least one randomised and controlled clinical trial |
| **IIa** | At least one controlled study, with witness, not randomised | **B** |
| **IIb** | At least one type of experimental study. |
| **III** | Descriptive studies, non-experimental, such as comparative studies, of correlation or case-control |
| **IV** | Reports of committees of experts, opinions or clinical experience of recognized authorities | **C** |
| **V** | Traditional use | **T** |

1. **Recommendations for classification**: the general guidelines of AHCPR, WHO and EMEA for natural active substances, provide the following recommendations for the support of their classification based on their safety and effectiveness:

|  |  |
| --- | --- |
| **Grade** | **Recommendation** |
| **A**  (Evidence level  Ia, Ib) | Requires at least one randomised trial with witness, published on the intended use. |
| **B**  (Evidence level  IIa, IIb, III) | Requires clinical trials but not randomised on the intended use. |
| **C**  (Evidence level  IV) | Requires evidence from expert committee reports or opinions or clinical experience of recognised authorities. |
| **T**  (Evidence level  V) | Requires justified support of ethno-medical and ethnobotanical usage reports, technical and scientific documentation, indexed publications or documents endorsed by a committee of experts, either, require bibliographical references or expert reports in demonstrating that the natural active substance in question has had medicinal use for a minimum period of 30 years preceding the date of application, of which at least 15 years in the Central American territory. At the request of the country in which the application for registration/enrollment for traditional use is submitted, the regulatory authority shall issue an opinion on the adequacy of the experience of traditional use of the natural active substance. The applicant shall provide appropriate documentation in support of its request for an opinion. |

**ANNEX 4**

**(Normative)**

**OFFICIAL BOOKS TO ESTABLISH QUALITY SPECIFICATIONS AND AS A SOURCE OF CONSULTATION**

The official books to use as a reference the Central American region in the field of natural products are as follows in all editions, supplements and volumes:

1. British Herbal Compendium.
2. Compendium of Monographs, published by the Board of Directors of Natural Medicinal Products of Canada.
3. British Herbal Pharmacopoeia.
4. Herbal Pharmacopoeia of Mexico.
5. American Herbal Pharmacopoeia.
6. Caribbean Plant Pharmacopoeia. TRAMIL. Robineau L. editor.
7. European Pharmacopoeia.
8. Japanese Pharmacopoeia.
9. French Pharmacopoeia.
10. Pharmacopoeia of the People's Republic of China.
11. Ayurvedic Pharmacopoeia and the Ayurvedic Form of India.
12. National Pharmacopoeia/Form of the United States
13. Swiss Pharmacopoeia.
14. German Pharmacopoeia.
15. Italian Pharmacopoeia.
16. Spanish Pharmacopoeia.
17. Monographs on Medicinal Uses of Plant Drugs of ESCOP.
18. Monographs of Selected Medicinal Plants of the WHO.
19. PDR for Herbal Medicine.
20. National Formulary of Medicinal Plants (Guatemala)
21. Alonso. J. R. 2006. Treaty of Phyto-medicine. Clinical and pharmacological bases. Pp: 690-695.
22. Vanaclocha, B., Cañigueral, S. editors. 2003 Phytotherapy. Formulary prescription. 4th Edition. Masson.
23. Other references with internationally recognized scientific basis.

**-— END OF THE TECHNICAL REGULATIONS--**