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PRODUCTS PHARMACEUTICALS PRODUCTS NATURAL MEDICINALS FOR HUMAN USE. HEALTH REGISTRATION REQUIREMENTS.

CORRESPONDENCE: This regulation has no correspondence with any document.

Edited by:

- Ministry of Economy, **MINECO**
- Salvadoran Technical Regulation Agency, **OSARTEC**
- Ministry of Development, Industry and Commerce, **MIFIC**
- Secretariat of Economic Development, **SDE**
- Ministry of Economy, Industry and Commerce, **MEIC**
- Ministry of Commerce and Industries, **ICIM**

REPORT

The respective technical regulatory technical committees through the entities of technical regulation of the member states that make up the Central American region, and their successors are the bodies responsible for conducting the study or the adoption of technical regulations They are made up of government representatives, agencies of consumer, academic and private sector protection.

This document was approved as Central American Technical Regulation RTCA11.03.64: 19 PHARMACEUTICAL PRODUCTS. NATURAL PRODUCTS MEDICINALS FOR HUMAN USE. HEALTH REGISTRATION REQUIREMENTS **,** by the Subgroups of Standardization Measures and Related Drugs and Products of the Central American Region The officialization of this technical regulation entails the approval by the Council of Economic Integration Ministers (COMIECO).

COMMITTEE PARTICIPATING MEMBERS

For Guatemala:
Ministry of Public Health and Social Assistance

For El Salvador:
National Directorate of Medicines

For Nicaragua:
Ministry of Health

For Honduras:
Health Regulation Agency

For Costa Rica:
Ministry of Health

For Panama:
Ministry of Health

one. OBJECT

Establish the conditions and requirements under which the sanitary registration of Natural medicinal products for human use for commercialization.

two. SCOPE

Applies to natural medicinal products for human use that manufacture or import, natural or legal persons for commercialization in the States Parties of the region Central American

Products to which synthetic active substances are added are excluded. chemical or isolated from natural material as responsible for pharmacological activity, as well as the pharmaceutical forms that are applied by the ophthalmic and parenteral route.

3. DOCUMENTS TO CONSULT

3.1 RTCA Pharmaceutical Products. Natural Medicinal Products for use Human. Labeling Requirements Valid.

3.2 RTCA Pharmaceutical Products. Natural Medicinal Products for use Human. Quality Verification. Valid.

3.3 RTCA Pharmaceutical Products. Natural Medicinal Products For Use Human. Good manufacturing practices. Valid.

Four. DEFINITIONS

4.1 Competent Authority: authority responsible for issuing the Certificate of Free Sale and Certificate of Good Manufacturing Practices for natural products Medicinal in each country or region.

4.2 Regulatory Authority: authority responsible for health regulation in each Country or region.

4.3 Good Manufacturing Practices : set of procedures and standards intended to ensure the uniform production of lots of natural products Medicines to meet quality standards.

4.4 Certificate of Good Manufacturing Practices: document issued by the competent authority of the country in which the manufacturing laboratory is located where it is certified that the laboratory complies with good manufacturing practices.

4.5 Free Sale Certificate: document issued by the competent authority of the country of origin or of origin, in which it certifies that the medicinal natural product has your current registration and you are authorized for sale or distribution in that country.

In the case of manufacturing by third parties or subsidiaries and the product is not marketed in the country of origin, may be issued by the competent authority of the holder's country.

4.6 Certificate of registration: official document issued by the competent authority that authorizes marketing a natural medicinal product.

4.7 Committee of experts: group of people who, due to their suitability, are recognized by the regulatory authority, to endorse the documents that support the use and security of a natural active substance or a medicinal natural product.

The formation of the group of experts will be convened by the regulatory authority, when I consider it necessary.

4.8 Manufacturing contract: legal document concluded between the owner of the product medicinal natural and the manufacturer in which the conditions, commitments and other circumstances for the manufacture of one or more products.

4.9 Natural drug **:** substance of natural origin and with activity that is used alone or combined in the elaboration of natural medicinal products.

4.10 Packaging or container: material used to protect in handling, storage and transport to the medicinal natural product.

4.11 Primary packaging or container: container or container in which it is placed directly the finished medicinal natural product.

4.12 Secondary packaging or packaging: final distribution and marketing package or packing material into which the primary container containing the Natural medicinal product in its definitive pharmaceutical form.

4.13 Specific epithet: Latinized name that accompanies the genre, to form the name Binomial of a species.

4.14 Stability studies: tests performed to determine the period of validity of the medicinal natural product in its original primary container and in conditions of specified storage.

4.15 Labeling: mandatory information included in the label, label, image or other descriptive or graphic matter that has been written, printed, stenciled or marked in relief, which is attached or included in the package of a medicinal natural product.

4.16 Excipient: substance without pharmacological action at the concentration used, which determines or modifies the consistency, shape, volume or physicochemical properties of the preparations of natural medicinal products.

4.17 Extract: preparations of liquid consistency (fluid extracts and tinctures), semi-solid (soft extracts) or solid (dry extracts), obtained from drugs natural.

4.18 Standardized extract **:** extract that provides a minimum level or specific range of one or more constituents, whether or not they have pharmacological activity, provided that this one maintains the identity of the natural drug from where it comes.

4.19 Manufacturing to third parties : domestic or foreign manufacturing carried out within the limits of a previous contracting between the holder of the medicinal natural product and the manufacturer, the owner being responsible for the product.

4.20 Expiration or expiration date **:** date established for each lot placed on the primary and secondary packaging until which the medicinal natural product is expected, Stored properly meet quality specifications.

4.21 Modality of sale: variants by means of which they can be marketed natural medicinal products, these being the following:

4.21.1 Prescription product under medical prescription or prescription product;

4.21.2 Over the counter product.

4.21.3 Retained prescription product.

4.22 Monograph of finished product: technical scientific description of the profile of Safety and efficacy, according to the level of evidence of a natural medicinal product.

4.23 Scientific name: binary name of the species, formed by genus and epithet specific.

4.24 Country of origin: country where the product is manufactured. In case of manufacturing Intervene more than one manufacturing laboratory, the country of origin is the one in which the manufacture of at least the bulk product.

4.25 Country of origin: country from which the country is distributed, conditioned or exported product. Provided that they intervene in the manufacturing process; at least until primary packing

4.26 Natural preparation: it is the one obtained from the natural raw material by fractionation process, solvent extraction, expression, distillation, purification, fermentation, concentration or any other physical or biological process.

4.27 Natural medicinal product **:** product processed, industrialized and labeled with medicinal properties, which contains in its formulation ingredients obtained from the plants, animals, minerals or mixtures of these. May contain excipients in addition to natural material Natural medicinal products to which substances are added

chemical synthesis active or isolated from natural material as responsible for the activity Pharmacological, they are not considered as natural medicinal products.

4.28 Traditional medicinal natural product: it is one whose use and safety of Natural active substances is justified by ethnomedicinal reports, documentation technical and scientific, indexed publications or documents endorsed by a committee of experts They are used by oral, topical or other route that does not require sterility.

4.29 Retained prescription product: it is the authorized natural medicinal product for marketed under a retained prescription, as applicable.

4.30 Responsible professional **:** pharmaceutical professional or pharmaceutical chemist, responsible for the sanitary registration process before the regulatory authority, authorized by the owner of the product or its legal representative through a power of attorney granted according to the legislation of each State Party.

4.31 Sanitary registration: approval procedure by the competent authority of a country for the commercialization of a medicinal natural product, once it has After the evaluation process related to quality, efficiency and safety.

4.32 Legal representative: natural or legal person residing in the country where it is processed the registration, authorized by the owner of the medicinal natural product, through a power of attorney granted in accordance with the legislation of each State Party, to respond to the regulatory authority

NOTE: in the case of El Salvador, the figure of the legal representative or proxy may be used .

4.33 Natural active substance **:** chemically defined substance or groups of substances, whose pharmacological action is known and is responsible for therapeutic effects present in The natural medicinal product. When the chemicals mentioned are unknown previously, the natural drug or the natural preparation is considered active substance.

4.34 Product holder or registration holder : natural or legal person who owns the product.

4.35 Traditional use : it is supported by documentary evidence that states that the natural drug that is used in a product, has been used for three or more decades For medicinal purposes.

4.36 Shelf life: period during which a product is expected, if stored correctly, keep the established specifications.

5. INGREDIENT ACCEPTANCE CATEGORIES IN A NATURAL MEDICINAL PRODUCT

5.1. Ingredients accepted:

5.1.1 Natural drugs

5.1.2 Natural preparations.

5.1.3 Combinations of any of the above.

5.1.4 Pharmaceutically accepted excipients.

5.2 Ingredients not accepted:

5.2.1 Isolated molecules of natural ingredients and synthetic or semi-synthetic compounds chemistry used as active ingredient, which by definition are excluded from products Natural medicinal

5.2.2 Natural substances prohibited in accordance with international recommendations or the regulation issued in each State Party.

5.2.3 Species identified as protected or endangered unless come from managed crops or upbringing.

5.2.4 Homeopathic ingredients (strains, mother tinctures and dilutions).

6. PHARMACEUTICAL FORMS

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

7. PROVISIONS FOR THE SANITARY REGISTRATION

7.1 For import, production, distribution, marketing, prescription, promotion and advertising, all natural medicinal products require prior registration health before the regulatory authority.

7.2 The sanitary registry of natural medicinal products will be valid for five years, which may be suspended or canceled when there are sanitary reasons of a character scientific, technical or legal duly justified.

7.3 Any official or legal document issued abroad must be legalized or Apostille legalize in compliance with the specific national regulations.

7.4 Any official or legal document required for registration must be current in the time of presentation The official documents will have the validity granted by the competent authority of the country where it is issued. In cases where the validity, this will be 2 years for the purposes of the registration process from the date of issue.

7.5 All official or legal documents must be submitted in original or legalized copy or Apostilled in accordance with the legislation of each State Party. The document must be present in Spanish / Spanish language or in case of presenting in another language, it must be accompanied by their respective translation issued in accordance with the legislation of each State party

7.6 No corrections are allowed in certifications or in official documents filed, unless supported by the same instance that issued the document original.

7.7 In those cases in which it applies and for the purposes of registering a natural product specific medicine, the applicant will be allowed to refer to documents current originals that are on file with the regulatory authority. In this case the Applicant must refer to the management in which the original document was delivered, presenting a simple photocopy of it.

7.8 The administrative procedure for the process of sanitary registration, renovation and modifications will be made in accordance with the internal legislation of each State Party.

7.9 Failure to comply with these regulations will result in the application of the established in the sanction regime of each State Party.

7.10 This Central American Technical Regulation of Pharmaceutical Products. products Natural Medicines for Human Use. Sanitary Registration Requirements, repeal only the provisions of the requirements for sanitary registration, renovation and modifications of natural medicinal products of the internal regulation of each State party

7.11 Correspond to the same record:

7.11.1 Different commercial presentations of medications with the same concentration and the same pharmaceutical form.

7.11.2 Medicines with the same qualitative-quantitative formula and different taste and / or color.

8. REQUIREMENTS FOR HEALTH REGISTRATION

8.1 Proof of payment.

8.2 Health registration application signed and stamped by the responsible professional, containing the detailed information Annex A.

8.3 Powers that accredit the legal and / or technical representation granted by the holder to the natural person (s) or legal entity (s) in accordance with the legislation of each country. (original or authenticated photocopy of the document).

8.4 Certificate of free sale of the product, issued by the competent authority of the country of origin or provenance.

8.5 Certificate of Good Manufacturing Practices, of each of the establishments involved in the manufacture of the product, when not included in the free sale certificate, declaring the pharmaceutical form and type of product to register, extended by the competent authority of the country or countries where it is carried out the manufacturing process, or equivalent document issued by the competent authority, document issued by the regulatory authority indicating that it conducts inspections periodic to the establishment but that does not extend the certificate of good practices of manufacture.

8.6 Manufacturing contract or otherwise the relative extract of the parts of the contract of manufacture, when applicable, in original or certified or certified photocopy of the legalized or apostilled document, containing at least the following information:

8.6.1 Signed by the holder and the manufacturer jointly or separately.

8.6.2 Commitment to compliance with good manufacturing practices.

8.6.3 Establish the conditions of production, analysis, when applicable or any other technical management related to these.

8.6.4 Should describe the handling of raw materials, conditioning material, bulk product and finished product and if rejected.

8.6.5 Allow the contractor to enter the contractor's premises (contracted) for audits

8.6.6 Allow the contractor (contracted) to enter the contractor's premises.

8.6.7 List each of the products or services of analysis object of the contract.

8.7 Complete qualitative and quantitative formula of the product per dose unit. I know must present in original signed and stamped by the professional responsible for the laboratory manufacturer or holder of the product, indicating:

8.7.1 Name (s) of the active substance (s):

8.7.1.1 Scientific name of the organism from which drugs or preparations are obtained natural, indicating the part or organ used.

8.7.1.2 Internationally accepted chemical name or denomination, for drugs minerals or their preparations.

8.7.2 Solvent used, in liquid extracts. If the solvent is ethanol, you must declare the percentage.

8.7.3 Drug / solvent or excipient ratio, in case of extracts or standardization 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 must be given according to the international measurement system (SI).

8.7.4 Qualitative composition of empty capsules.

8.7.5 Qualitative composition of printing inks in capsules, dragees and coated tablets

8.7.6 In the case of pharmaceutical forms with a topical route of administration, the formulation should be presented for each g, 100 g, mL or 100 mL or percentage.

8.8 Monograph of the finished product.
The monograph must correspond to the pharmaceutical form of the product to be registered, which It must contain the following information:

NOTES:

1) When the information requested is not applicable to the product's own characteristics, it may ignore in the monograph.
2) For Panama, they must include precautions regarding excipients, which are published through internal resolution

8.8.1 Product name.

8.8.2 Composition:

8.8.2.1 Scientific name of the organism from which drugs or preparations are obtained natural, indicating the organ used.

8.8.2.2 Internationally accepted chemical name or denomination, for drugs minerals or their preparations.

8.8.3 Pharmaceutical form.

8.8.4 Form of preparation.

8.8.5 Pharmacological information, including:

8.8.5.1 Indications.

8.8.5.2 Contraindications.

8.8.5.3 Precautions and warnings.

8.8.5.4 Maximum time of use, when applicable.

8.8.5.5 Interactions.

8.8.5.6 Adverse effects.

8.8.5.7 Dose and route of administration.

8.8.5.8 Recommendation in case of overdose or abuse, when applicable.

8.8.5.9 Bibliographic references.

8.8.5.10 Monograph revision date.

8.9 Safety and efficacy information in accordance with Annex C of this technical regulation

8.10 Analytical methodology.

8.11 Specifications of the finished product.

8.12 Labeling of primary, secondary and insert packaging or packaging (as applicable), in original or its projects, according to current regulations.

8.13 Stability study report.

NOTES:

1) As long as the RTCA Stability Studies for Natural Medicinal Products does not take effect, it will require the report of analysis of the physical, chemical and microbiological tests according to the established in the RTCA Pharmaceutical Products. Natural Medicinal Products for Human Use. Quality Verification, current.
2) In the case of Panama, a useful life period of more than 24 months will not be granted.

8.14 A copy of the finished product, for pharmaceutical evaluation.

8.15 Samples of original finished product, according to harmonized quantity to make the analyzes, according to the RTCA Pharmaceutical Products. Natural products Medicinal products for human use. Quality Verification, current.

8.16 Standards or standardized raw material for analysis, when the Analysis methodology requires it.

NOTES:

1) Requirement 8.14 will not apply in the case of Guatemala since the analysis samples are used.
2) Requirements 8.15 and 8.16 will be requested after the registration of the medicinal natural product for the case from Costa Rica, El Salvador and Nicaragua.

9. REQUIREMENTS FOR THE RENEWAL OF THE SANITARY REGISTRY

The renewal of the sanitary registry of a natural medicinal product may be managed by At least three months before its expiration.

Once the sanitary registration has expired, the product cannot be marketed. Be processed as a new record.

If during the 6 months after the expiration of the registration of the natural product medicinal, the interested party requests to keep the assigned number presenting the cause justified, the regulatory authority will keep the original number, however, during This period, you will not be able to market it.

Renewal will not be granted, until the requested post-registration changes have been approved.

9.1 When the product maintains the information and characteristics that have been Approved during the validity of the registration, when requesting renewal they must present:

9.1.1 Proof of payment for registration renewal.

9.1.2 Application for renewal of sanitary registration signed and stamped by the professional responsible containing the detailed information in Annex A.

9.1.3 Affidavit issued by the holder or his legal representative or by the professional responsible for the registration by means of power issued by the owner of the product, that the product information and features have not changed since the last request for modification submitted to the regulatory authority.

9.1.4 Certificate of free sale of the product, issued by the competent authority of the country of origin or provenance.

9.1.5 Certificate of good manufacturing practices of each of the establishments involved in the manufacture of the product, when it is not included in the certificate of free sale, declaring the pharmaceutical form and type of product to be renewed, extended by the competent authority of the country or countries where the manufacturing process is carried out or equivalent document issued by the competent authority, or document issued by the regulatory authority indicating that it conducts periodic inspections at establishment but does not extend the certificate of good manufacturing practices.

9.1.6 Stability Study Report confirming the approved lifespan.

NOTES:

1) As long as the RTCA Stability Studies for Natural Medicinal Products does not take effect, it will require the report of analysis of the physical, chemical and microbiological tests according to the established in the RTCA Pharmaceutical Products. Natural Medicinal Products for Human Use. Quality Verification, current.

2) In the case of Panama, a useful life period of more than 24 months will not be granted.

9.2 In cases where the medicinal natural product presents modifications to the health record that are not known to the regulatory authority may be requested simultaneously to the renewal.

In the same way, if the affidavit cannot be presented, in both cases they must meet the following requirements:

9.2.1 Proof of payment.

9.2.2 Application for renewal of sanitary registration and of the signed and sealed by the responsible professional, containing the detailed information Annex A.

9.2.3 Powers that accredit the legal and / or technical representation granted by the holder to the natural person (s) or legal entity (s) according to the legislation of each country. (original or authenticated photocopy of the document).

9.2.4 Certificate of free sale of the product, issued by the competent authority of the country of origin or provenance.

9.2.5 Certificate of good manufacturing practices, in accordance with the provisions of the 8.5 of registration requirements.

9.2.6 Manufacturing contract, when applicable, in accordance with 8.6 of registration requirements

9.2.7 Complete qualitative and quantitative formula of the product per dose unit, in accordance with paragraph 8.7 registration requirements.

9.2.8 Specifications of the finished product.

9.2.9 Labeling of primary, secondary and insert packaging or packaging (as applicable), in original as it is being marketed, according to current labeling regulations.

NOTE: When the product has not been commercialized, the print art project of the product will be accepted. primary and secondary packaging in Spanish, accompanied by an affidavit from the holder of the product indicating that the product has not been marketed.

9.2.10 Stability Study Report confirming the period of useful life.

NOTES:

1) As long as the RTCA Stability Studies for Natural Medicinal Products does not take effect, it will require the report of analysis of physical, chemical and microbiological tests in accordance with the established in the RTCA Pharmaceutical Products. Natural Medicinal Products for Human Use. Quality Verification, current.
2) In the case of Panama, a useful life period of more than 24 months will not be granted.

9.2.11 According to the requested modification, you must present the documents according to Annex B.

10. CAUSES OF NON GRANTING OF THE SANITARY REGISTRY.

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

10.1 Do not comply with the requirements established in the RTCA .

10.2 The documentation submitted according to current technical regulations is incomplete, incorrect or not current.

10.3 The formula contains ingredients reported as unsafe, or in doses and routes not allowed.

10.4 The formula contains ingredients with antagonistic therapeutic effects.

10.5 There is a discrepancy between the analytical result and the documentation presented.

NOTE: This case will not apply in the case of Costa Rica, El Salvador, Honduras and Nicaragua.

10.6 Lacking in its dosage of therapeutic efficacy or safety as indicated in the table in Annex C: Classification of natural active substances based on the safety and efficacy.

10.7 That the studies or research presented in support of the application be incomplete, or insufficient to demonstrate the quality, safety and efficacy of the product as indicated in the table in Annex C: Classification of natural active substances based on safety and effectiveness.

eleven. CAUSES OF CANCELLATION OF THE SANITARY REGISTRY

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

11.1 Check that the product proves to be harmful or unsafe under the conditions normal use.

11.2 For falsification or alteration of the documents submitted to the authority Regulatory

11.3 When it is shown that the product does not have the quantitative composition or qualitative authorized or when quality and stability guarantees are breached declared in the file, following due process according to the legislation of each State party

11.4 When requested by the product owner.

11.5 It has been demonstrated with conclusive scientific evidence that the product does not have The therapeutic properties with which it was initially registered.

11.6 That prior warning is continued breaching the RTCA Products Pharmacists Natural Medicinal Products for Human use. Requirements of Labeling, in its current version

12. MODIFICATIONS TO THE SANITARY REGISTRY

Any modification to the information that is made after the sanitary registration must comply with the provisions of Annex B.

When there are changes of natural active substances, pharmaceutical form and Product concentration, must submit a new record.

13. SURVEILLANCE AND VERIFICATION

The supervision and verification of this technical regulation corresponds to the authorities Regulatory States Parties.

ANNEX A
(NORMATIVE)
APPLICATION FOR THE SANITARY RECORD. REQUIRED INFORMATION

one. Product dates

1.1 Product name.
1.2 Name of natural active substances.
1.3 Pharmaceutical form
1.4 Route of administration.
1.5 Product presentation.
1.6 Proposed lifespan.
1.7 Modality of sale.
1.8 Registration category (new, renewal).

two. Manufacturer and conditioner data

2.1 Name and country of the laboratory (s) involved in manufacturing.
2.2 Address, telephone and email.
2.3 Manufacturing stage.
2.4 Health license number or operating health permit and date of expiration, (when national).

3. Product holder data

3.1 Name
3.2 Address, telephone, and email.
3.3 Country

Four. Data of the distributor (s)

4.1 Name of the distributor (s).
4.2 Address, telephone, fax and email.
4.3 Health license number and expiration date.

5. Data of the legal representative

5.1 Name
5.2 Identity document number.
5.3 Address, telephone, and email.

6. Responsible professional data

6.1 Name
6.2 Identity document number.
6.3 Address, telephone, and email.
6.4 Collegiate or pharmaceutical chemical registration number.

7. Legend that gives you the character of an affidavit in the application.

ANNEX B
(NORMATIVE)
REQUIREMENTS FOR CHANGES TO THE SANITARY REGISTRY

B1) Modifications that require prior approval by the regulatory authority.

MODIFICATION	REQUIREMENTS
1. In the commercial presentation.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current. **4.** Document issued by the holder or his legal representative to declare the change.
2. In the name of the product	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Document issued by the holder or his legal representative to declare the change of Name. **4.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current.
3. Social name of the manufacturer, packer or holder	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Legal document proving the change. **4.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human Use. Labeling Requirements, current.
4. In the monograph and insert.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Monograph and insert updated with requested changes. **4.** Bibliographic reference or otherwise, studies as established in the requirements Registration supporting the change. **5.** Document issued by the holder or his

	legal representative that accredits the change.
5. In the period of useful life.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Stability study report confirming the proposed lifespan.

		NOTES: 1) As long as the RTCA Studies of Stability for Natural Medicinal Products, is will require the physical evidence analysis report, chemical and microbiological according to the established in the RTCA Pharmaceutical Products. products Natural Medicinal For Use Human. Quality Verification, current. 2) In the case of Panama, a period of shelf life greater than 24 months.
		4. Document issued by the holder or his legal representative that accredits the change.
6. In the terms storage.	from	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Stability study report to support The requested conditions.
		NOTES: 1) As long as the RTCA Studies of Stability for Natural Medicinal Products, is will require the physical evidence analysis report, chemical and microbiological according to the established in the RTCA Pharmaceutical Products. products Natural Medicines for Human use. check of Quality, in force. 2) In the case of Panama, a period of shelf life greater than 24 months
		4. New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current. **5.** Document issued by the holder or his legal representative that accredits the change.
7. Primary packer		**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Certificate of good manufacturing practices of the new packer.

		4. Contract with the new packer, in case of third party manufacturing. **5.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current. **6.** Affidavit stating that

they maintain the same conditions regarding the Qualitative-quantitative formula, type and material of primary packing, process and place of Manufacture of the registered product.

7. Document issued by the holder or his legal representative that accredits the change.

NOTES:

1) As long as the RTCA Studies of Stability for Natural Medicinal Products, is will require the physical evidence analysis report, chemical and microbiological according to the established in the RTCA Pharmaceutical Products. products Natural Medicines for Human use. check of Quality, in force.
2) In the case of Panama, a period of shelf life greater than 24 months.

8. From secondary packer	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Certificate of good manufacturing practices of the new packer. **4.** Contract with the new packer, in case of third party manufacturing. **5.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human Use. Labeling Requirements, current. **6.** Document issued by the holder or his legal representative that accredits the change.
9. Type of packing material primary or container-closure system.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Stability study report.

NOTES:

1) As long as the RTCA Studies of Stability for Natural Medicinal Products, is will require the physical evidence analysis report,

chemical and microbiological according to the established in the RTCA Pharmaceutical Products. products Natural Medicines for Human use. check of Quality, in force.
2) In the case of Panama, a period of shelf life greater than 24 months.

4. Specifications of the primary packaging or container-closure system.

5. Document issued by the holder or his legal representative that accredits the change.

10. Adding a new package primary	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Stability studies report for the packaging requested. NOTE: Until RTCA goes into effect Stability Studies for Natural Products Medicinal, the Analysis Report of the physical, chemical and microbiological tests according to established in the RTCA Pharmaceutical Products. Natural Medicinal Products for Human use. Quality Verification, in force, to demonstrate that the Product is within the specifications presented in the registration dossier for the new packing. **4.** New original container labels primary, secondary (when applicable) or its Projects according RTCA products Pharmacists Natural Medicinal Products for human use. Labeling Requirements, valid. **5.** Specifications of the primary packaging. **6.** Document issued by the holder or his legal representative that accredits the change. NOTES: 1) As long as the RTCA Studies of Stability for Natural Medicinal Products, is will require the physical evidence analysis report, chemical and microbiological according to the established in the RTCA Pharmaceutical Products. products Natural Medicinal for Use Human. Quality Verification, current. 2) In the case of Panama, a period of shelf life greater than 24 months.
11. Holder	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable.

	3. New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current. **4.** Legal document proving the change attaching the new powers. **5.** Contract in accordance with paragraph 8.6 in case Manufacturing by third parties.
12. In case of manufacturing by third parties:	**1.** Proof of payment. **2.** Application signed and stamped by the professional

	responsable.
to) Change of manufacturer b) Change of manufacturer and country of origin.	**3.** Certificate of free sale of the product. **4.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current. **5.** Certificate of good manufacturing practices from the new manufacturer. **6.** Stability study report. NOTE: Until RTCA goes into effect Stability Studies for Natural Products Medicinal, the analysis report of the physical, chemical and microbiological tests according to established in the RTCA Pharmaceutical Products. Natural Medicinal Products for Human Use. Quality Verification, to demonstrate that the Product is within the specifications presented in the registration dossier for the product manufactured in the new plant. **7.** A copy of the finished product. **8.** Samples of the finished product for analysis according to what is established in the RTCA Pharmaceutical products. Natural products Medicinal products for human use. Verification of Quality, current. NOTE **:** In the case of Costa Rica and El Salvador does not apply the presentation of samples, because post-analysis is done approval. **9.** Analytical methodology. **10.** Contract with the new manufacturer of compliance with numeral 8.6. **11.** Document issued by the holder or his legal representative that accredits the change.
13. Modality of sale	**1.** Proof of payment. **2.** Application signed and stamped by the professional

	responsable. **3.** Information justifying the change issued by the owner or his legal representative. **4.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human Use. Labeling Requirements, current.
14. Change of excipients or change in their concentration.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Qualitative quantitative formula per unit dose

	4. Stability study report. NOTES: 1) As long as the RTCA Studies of Stability for Natural Medicinal Products, is will require the physical evidence analysis report, chemical and microbiological according to the established in the RTCA Pharmaceutical Products. products Natural Medicinal For Use Human. Quality verification, current. 2) In the case of Panama, a period of shelf life greater than 24 months. **5.** Samples of finished product with its specifications, when applicable. NOTE **:** In the case of Costa Rica and El Salvador, the presentation of samples, because it makes post-analysis approval. **6.** Technical justification for the change. **7.** Analytical methodology of the finished product, when applicable **8.** Specifications of the finished product updated, when applicable. **9.** Document issued by the holder or his legal representative that accredits the change.
15. Information on labeling primary and secondary	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** New original container labels primary, secondary or its projects according RTCA Pharmaceutical Products. products Natural Medicines for Human use. Labeling Requirements, current. **4.** Technical justification for the change issued by the holder or his legal representative.
16. Manufacturing site within a same country.	**1.** Proof of payment. **2.** Application signed and sealed. **3.** Certificate of good manufacturing practices. **4.** Affidavit of the owner of the product or legal representative stating that Manufacturing conditions have not changed. **5.** Document issued by the holder or his legal representative that accredits the change.
17. Of legal representative or responsible professional.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Power granted according to the legislation of

	each State Party that accredits the change.
18. Change of pharmaceutical form, route of administration, concentration and species of the active substance.	**1.** A health record must be performed.
19. Change or update in specs of the product finished.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** New specifications of the finished product that complies with the provisions of the RTCA Quality Verification, current. **4.** Justification supporting the requested change accompanied by scientific information in the That such change is supported. **5.** Document issued by the holder or his legal representative to declare the change.
20. Change or update in the analytical methodology.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Full description of the analysis methods (when it is not pharmacopeic). **4.** Validation documentation **5.** Justification supporting the change. **6.** Document issued by the holder or his legal representative to declare the change.
21. Extension of indications therapeutic	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Therapeutic monograph and updated insert. **4.** Clinical studies that support the new indication. (when applicable). **5.** Document issued by the holder or his legal representative to declare the change.

B2) Modifications that must be notified to the regulatory authority and not Require prior approval.

MODIFICATION	REQUIREMENTS
1. Material or dimensions of secondary package.	**1.** Notification signed and stamped by the professional responsable. **2.** Document issued by the holder or his legal representative to declare the change. **3.** Original packaging or your projects.
2. Label design primary and secondary packaging.	**1.** Notification signed and stamped by the professional responsable. **2.** Document issued by the holder or his legal representative to declare the change. **3.** Original packaging or your projects.
3. Discontinuation from	**1.** Notification signed and stamped by the professional

Registered presentations	responsable. **2.** Document issued by the holder or his legal representative to declare the change.
4. Change or extension of distributor.	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Legal document issued by the holder or his legal representative that endorses the change or the extension.
5. Change in information product safety	**1.** Proof of payment. **2.** Application signed and stamped by the professional responsable. **3.** Document that supports the change. **4.** Monograph and insert with the indicated change When the product includes it.

ANNEX C
(NORMATIVE)
CLASSIFICATION OF NATURAL ACTIVE SUBSTANCES BASED ON THE SAFETY AND EFFICACY

1. Security levels: based on the general guidelines of the Policy Agency and United States Health Research (AHCPR), World Organization of the Health (WHO / WHO) and the European Medicines Agency (EMA) substances Natural assets are classified according to their safety and effectiveness as follows shape:

Level of evidence	Type of evidence	Grade
Ia	Meta-analysis of randomized controlled trials	**TO**
Ib	At least one randomized controlled clinical trial	
IIa	At least one controlled study, with witness, not randomized	

IIb	Minimum of one type of experimental study.	**B**
III	Descriptive, non-experimental studies, such as studies comparatives, correlation or case-control	
IV	Reports of expert committees, opinions or clinical experience of recognized authorities	**C**
V	Traditional use	**T**

2. Recommendations for classification: the general guidelines of AHCPR, WHO and EMEA for natural active substances, establish the following recommendations for the support of its classification based on its safety and efficacy:

Grade	Recommendation
TO (Level of evidence Ia, Ib)	Requires at least one randomized witnessed trial About the declared use.
B (Level of evidence IIa, IIb, III)	Requires clinical but not randomized trials About the declared use.
C (Level of evidence IV)	Requires evidence from reports or opinions of expert committees or clinical experience of authorities recognized.
T (Level of evidence V)	It requires the justified support of ethnomedical reports and ethnobotanical utilization, technical documentation and scientific, indexed publications or documents endorsed by a committee of experts, or requires bibliographic references or expert reports proving that the Natural active substance in question has had medicinal use for a minimum period of 30 years prior to the date of the request, of which at least 15 years in the territory Central American At the request of the country in which the application for registration / registration for traditional use, the authority regulator will issue an opinion on the sufficiency of the experience of traditional use of the natural active substance. The Applicant will present the appropriate documentation in support of their Opinion request.

ANNEX D
(NORMATIVE)
OFFICIAL BOOKS TO ESTABLISH THE SPECIFICATIONS OF QUALITY AND AS A SOURCE OF CONSULTATION

The official books to use as a source of consultation in the Central American region in Natural products are the following in all editions, supplements and volumes:

a) British Herbarium Compendium.
b) Compendium of Monographs, published by the Products Administration Council Natural Medicines of Canada.
c) British Herbal Pharmacopoeia.
d) Herbal Pharmacopoeia of the United Mexican States.
e) American Herbal Pharmacopoeia.
f) Caribbean Vegetable Pharmacopoeia. TRAMIL Robineau L. editor.
g) European Pharmacopoeia.
h) Japanese Pharmacopoeia.
i) French Pharmacopoeia.

j) Pharmacopoeia of the People's Republic of China.
k) Ayurvedic Pharmacopoeia and the Ayurvedic Form of India.
l) Pharmacopoeia / National Form of the United States.
m) Helvetic Pharmacopoeia.
n) German Pharmacopoeia.
o) Italian Pharmacopoeia.
p) Spanish Pharmacopoeia.
q) Monographs of Medicinal Uses of Vegetable Drugs of ESCOP.
r) Monographs of Selected Medicinal Plants of WHO.
s) PDR for Herbal Medicine.
t) National Vademecum of Medicinal Plants (Guatemala).
u) Alonso. JR 2006. Phytomedicine Treaty. Clinical and pharmacological bases. Pp: 690-695.
v) Vanaclocha, B., Cañigueral, S. editors. 2003 Phytotherapy. Vademecum of prescription. 4th. edition. Masson
w) Other references with internationally recognized scientific basis.

- END OF THE CENTRAL AMERICAN TECHNICAL REGULATIONS -