PANDRH Series - Technical Document No. 10

Pan American Network on Drug Regulatory Harmonization

Working Group on Medicines Registration

Requirements for Medicines Registration in the Americas

Pan American Health Organization
Regional Office of the World Health Organization

110
1902 - 2012

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Washington, DC, June 2013

Also published in Spanish (2013) with the title:
Requisitos para el registro de medicamentos en las Américas
ISBN 978-92-75-31757-0

PAHO HQ Library Cataloguing-in-Publication Data

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Pan American Health Organization.

Requirements for Medicines Registration in the Americas. Washington, DC : PAHO, 2013.

(Pan American Network on Drug Regulatory Harmonization - PANDRH, Technical Document n.10).

1. Pharmaceutical Services - legislation & jurisprudence. 2. Pharmacy Administration.
3. Legislation, Pharmacy. 4. Research Report. 5. Americas. I. Title.

ISBN 978-92-75-11757-6 (NLM Classification : WA 730 DA1)

Discussed and approved by the VI Pan American Network on Drug Regulatory Harmonization Conference (PANDRH), July 2011, Brasilia/DF, Brazil.

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Abbreviations and Acronyms

API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical Classification System
BSE	Bovine Spongiform Encephalopathy
CAS	Chemical Abstract Service
CPP	Certificate of Pharmaceutical Product (Pursuant to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce)
CSF	Certificate of Free Sale
E	Excipient
FP	Finished Product
GMP	Good Manufacturing Practice
INN	International Non-proprietary Name
IUPAC	International Union of Pure and Applied Chemistry
NRA	National Regulatory Authority
OTC	Over the counter
PAHO	Pan American Health Organization
PANDRH	Pan American Network on Drug Regulatory Harmonization
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme
SPC	Summary of Product Characteristics
WHO	World Health Organization

Glossary

Active Pharmaceutical Ingredient (API):
Any substance or mixture of substances used in a medicine in order for it to perform pharmacological activity or have other direct effects on the diagnosis, cure, attenuation, treatment, or prevention of disease or for it to have a direct effect on the restoration, correction, or modification of physiological functions in humans.

Bioequivalence:
Two products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives. Their bioavailability in terms of peak concentration and time (C_{max} and T_{max}) and total exposure (area under the curve, AUC), after administration in the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Biological product:
A product used for the purposes of prevention (vaccines), treatment (cytokines, hormones), or in vivo diagnosis (monoclonal antibodies) of certain diseases. Biologicals are obtained from living organisms or their tissues. They include viruses, therapeutic sera, toxins, antitoxins, vaccines, blood, blood components or derivates, allergenic products, hormones, colony-stimulating factors, cytokines, antibodies, etc. Their sources and manufacturing methods vary: cell cultures from microorganisms, extractions from biological tissues, recombinant DNA techniques, transgenesis, hybridoma techniques, introduction of microorganisms into embryos or animals, etc.

Container closing system (also referred to as a container system):
This is the sum total of the components of the container that both contains and protects the pharmaceutical dosage form. This includes the primary container and the secondary container, if the latter is designed to provide additional protection for the finished product.

Dosage form:
Form or physical state in which a product is prepared to facilitate its fractionation, dosage, administration, or use.

Efficacy:
Extent to which medicine treatment produces a beneficial result measured in the context of controlled clinical trial. This result should be measured not only on surrogate variables (such as decreased blood pressure, HbA1c glycaemia, increased density) but also in clinically relevant variables such as rate of myocardial infarction, stroke, kidney disease, decreased risk of fractures, etc.

Excipient:
A substance or mixture of substances, in concentrations present in a pharmaceutical form, with no pharmacological activity and whose function is to ensure stability, bioavailability, acceptability and feasibility of administration of the active pharmaceutical ingredient(s) of the medicine.

Expiration date:
The date given on the individual container (usually on the label) of a product up to and including which the API and FPP are expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

Final bulk product:
Every product that has gone through all stages of processing, including dosage form, except final packaging.

Finished product:
This is the final dosage form that has gone through all manufacturing stages, including packaging into the container and final packaging.

Good Manufacturing Practices (GMPs):
A set of procedures and practices to guarantee the uniform and controlled production of lots of pharmaceutical products, based on quality standards appropriate to their use, pursuant to the conditions established for their marketing. Also known as Adequate Manufacturing Practices or Good Manufacturing Practices (GMPs).

Known medicines:
See *Multisource medicine or pharmaceutical product*.

Legal representative in the country:
it is related to the company who represents the product, who is in charge of the registration and/or marketing in the country.

Lot (batch):
A quantity of raw material, packaging material, or product manufactured in a process or series of processes in a way that is homogeneous. In order to control the finished product, a lot of a pharmaceutical product includes all units of a dosage form produced from the same initial mass of materials that has undergone a single series of manufacturing operations or a single sterilization procedure—or, in the case of a continuous production process, all the units made within a given time period.
Note: In order to perform certain processing steps may be necessary to divide a lot in various sublots, and then join them to form a final homogeneous lot. If continuous production, the lot must correspond to a definite specific portion of production, characterized by expected homogeneity.

Marketing authorization:
See *Registration*.

Multisource medicine or pharmaceutical product:
A pharmaceutically equivalent or a pharmaceutically alternative product that may or may not be therapeutically equivalent. The therapeutically equivalent multisource pharmaceutical products are interchangeable.

Pharmaceutical alternative:
The products are pharmaceutical alternatives if they contain the same molar amount of the same Active Pharmaceutical Ingredient may differ in dosage form and/or its salt or ester. Pharmaceutical alternatives deliver the same Active Pharmaceutical Ingredient fraction by the same route of administration but are not pharmaceutical equivalents. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

Pharmaceutical development of a product:
This refers to all studies conducted to demonstrate that the dosage, formulation, manufacturing process, and container-closure system, as well as the microbiological and physicochemical characteristics are appropriate for the proposed objective.

Pharmaceutical equivalents:
Medicines that contain the same Active Pharmaceutical Ingredient(s), in the same dosage form, for the same route of administration, and are identical in potency or concentration.

Pharmaceutical or Galenic development of a product:
This refers to all studies conducted to demonstrate that the dosage, formulation, manufacturing process, and container closing system, as well as the microbiological and physicochemical characteristics are appropriate for the proposed objective.

Product to register:
The medicine to be registered.

Registration or health registration:
This is the health procedure whereby the National Regulatory Authority grants authorization for the nationwide marketing and distribution of the product in question, based in the assessment of the evidence supporting its quality, efficacy and safety. It corresponds to the Marketing Authorization.

Safety:
This parameter is an inverse measure of risk, depends on the adverse effect profile of the medicine evaluated in case control, cohort, Pharmacovigilance Programs, case report and reporting of series of cases.

Shelf life:
Period of time during which a medicine, if stored properly, meets established specifications determined by the corresponding stability study. The validity period is used to set the expiration date of each batch. It is also called validity period.

Therapeutic alternative:
See *Pharmaceutical alternative*.

Useful life:
See *Shelf-life*.

Vaccine:

This is an immunogen administered to stimulate the immune system in order to prevent, reduce, or provide therapy against a given disease or infection. Vaccines can be preparations of attenuated viruses, bacteria, or parasites; inactivated complete organisms from crude fractions or purified immunogens, including those derived from recombinant DNA in host cells, conjugates formed by covalent links of components, synthetic antigens, polynucleotides (e.g. plasmid DNA vaccines), living cells from vectors expressing specific heterologous immunogens, or immunogen-activated cells. There are also combinations of vaccines or immunogens produced from those mentioned above.

Validation:

This involves a series of documented procedures or actions based on the principles of the Good Manufacturing Practices, which demonstrate that the processes, equipment, materials, activities, or systems meet predetermined specifications and quality requirements.

Introduction

This document comprises the requirements for the initial registration of medicines (marketing authorization) in the Americas, prepared by the Working Group on Medicines Registration of the Pan American Network on Drug Regulatory Harmonization (PANDRH). Its purpose is to provide requirements for establishing regulations and regulatory tools that will contribute to the harmonization process of medicines registration to ensuring the efficacy, quality and safety of medicines to be available in the countries of our Region.

National standards shall be established in keeping with each country's legislation, and whenever pertinent, appropriate changes will be made in order to adhere as much as possible to these requirements.

The information must be presented in the language of the country where the medicines are being registered.

These requirements shall be applicable to the following types of medicines:

a) Active Pharmaceutical Ingredient (API) with known formulation.

b) Known Active Pharmaceutical Ingredient (API), presented with a new:

- Combination of active pharmaceutical ingredients.
- Salt, ester, isomer, complex, or derivative.
- Dosage form and route of administration.
- Strength that deviates from the approved dosage range.

c) New Active Pharmaceutical Ingredient (API).

There are medicines, such as radiopharmaceuticals and medical gases, which due to their specificities, in addition to complying with these guidelines, must also comply with additional requirements.

These requirements will not be applicable to the following types of products:

a) Vaccines.

b) Products obtained by means of recombinant DNA.

c) Monoclonal antibodies.

d) Products obtained from human blood or blood components.

e) Other biological products.

It is recommended that a valid registration period of five years, renewable by successive periods of the same length, be established. The National Regulatory Authority (NRA) may withdraw the product due to a loss of effectiveness or therapeutic validity, or due to medicine's safety

or quality issues, according to health risk criteria. Variations in registration must be reported or authorized by the NRA, as applicable.

The specific requirements and guidelines deemed necessary for implementing these guidelines shall be developed by the working group at a future date.

In keeping with the format found in other similar guidelines of the Pan American Network on Drug Regulatory Harmonization (PANDRH), this document consists of four (4) modules and two (2) annexes.

- Module 1: Administrative and legal information.
- Module 2: Quality information.
- Module 3: Nonclinical reports.
- Module 4: Clinical reports.
- Annex 1: Summary of Product Characteristics (SPC).
- Annex 2: Information on labelling and package inserts.

Module 1: Administrative and Legal Information

Each country has its own application form to request health registrations, pursuant to its own legislation. At a minimum, the health registration application form should contain the following information:

1.1 Module table of contents.

There will be a table of contents of all documents presented in this module.

1.2. Medicine characteristics.

1.2.1. Name(s) of the Active Pharmaceutical Ingredient(s) (API): they must be presented according to the International Non-proprietary Names System (INN) and the Anatomical Therapeutic Chemical Classification System (ATC).

1.2.2. Brand name: it is the name under which the medicine will be marketed, if applicable. The name cannot suggest therapeutic indication or induce consumption.

1.2.3. Composition: the complete qualitative and quantitative formulation, expressed in units of weight or volume using the decimal metric system or conventional units recognized internationally, specifying dosage or dosage unit.

1.2.4. Dosage form: indicate the dosage form, for example: injectable solution, lyophilized powder for injectable suspension.

1.2.5. Route of administration: specify the route of administration.

1.2.6. Medicine packaging: state the content or amount of the medicine and the type of primary package (container-closure system) and secondary package, whether it will be distributed in a single-unit or multi-unit pack, and dispensing requirements. Any additional accessory—for example, a transfer device— must be indicated.

1.2.7. Description and interpretation of the lot or batch code: it is any combination of letters, figures, or both, used to identify the medicine during manufacturing or distribution.

1.2.8. Expiration date: in order to ensure its proper interpretation, the expiration date cannot appear in coded form.

1.2.9. Dispensing requirement: must specify:

a) Classification in the list of narcotic and psychotropic medicines, if applicable.

b) Dispensing without a prescription.

c) Dispensing with a prescription, specifying the type of prescription, and need for the dispensing agent to retain a copy of the prescription.

d) Restrictions on use: for exclusive use in clinics or hospitals.

1.2.10. Storage conditions: indicate the proper conditions for storing the product, indicating temperature, humidity, light, or any other necessary condition for non-reconstituted or reconstituted forms, as appropriate.

1.2.11. Conditions for handling and transport, as appropriate.

1.2.12. Shelf life proposed for the product, both non-reconstituted and reconstituted, when applicable.

1.3 Legal documentation.

Submit all legal information duly certified by the appropriate entity:

1.3.1. Technical director/health professional responsible: this is the technical professional responsible for the product in the country where the medicine is being registered. The following must be submitted:

a) Document issued by the holder of the medicine registration, clearly indicating all the information for the professional appointed as technical director, who shall be the technical expert responsible for the product in the country. It should state his/her name, address, telephone number, fax number, e-mail address, licensing number in the professional body with which she/he is affiliated, and the number of his/her academic degree.

b) Document issued by the competent health authority, accrediting the director responsible for the product.

1.3.2. Medicine's marketing authorization holder: state the full name of the medicine's registration or marketing authorization holder or owner, providing full address, telephone number, fax number, and e-mail address.

a) A document or written communication bearing the business name of the Marketing Authorization Holder must be provided, accrediting legal representation before the appropriate Medicine National Regulatory Authority (NRA).

b) This information must be submitted when the marketing authorization holder requests the registration of a medicine before the NRA for the first time; it is not necessary to submit it for subsequent variation requests for registered medicine. The information must be updated whenever there are changes made to it.

1.3.3. Legal representative in the country: this refers to the company that represents the product, responsible for its registration and/or marketing in the country. Full name, address, telephone number, fax number, and e-mail address must be provided. Additionally, the following must be submitted:

a) A document or written communication issued by the medicine's marketing authorization holder, authorizing the company or institution to represent it,

and empowering it to submit the corresponding registration applications and to market the authorized products in the country, when applicable.

b) This information must be submitted when the marketing authorization holder requests the registration of a medicine for the first time; it is not necessary to submit it subsequent variation requests for registered medicine. The information must be updated whenever there are changes made to it.

1.3.4. Manufacturer of the Active Pharmaceutical Ingredient (API)(s): indicate the names, addresses, telephone numbers, fax numbers, and e-mail addresses of the laboratories that manufacture the Active Pharmaceutical Ingredients, when applicable.

1.3.5. Manufacturer of the finished product: indicate the name, addresses, telephone numbers, fax numbers, and e-mail addresses of all laboratories that manufacture the final product and submit the following information and documents, including contracted laboratories, even if they are different from the registration holder:

a) In cases where there is more than one manufacturer, specify the following:

- The main manufacturer.
- The stages or steps in which each one is involved.

b) If the manufacturer(s) is/are not the medicine's marketing authorization holder, the legal document indicating the relationship between the two must be submitted.

c) Certificate of Good Manufacturing Practices (GMP) from the manufacturer(s) involved in the medicine's manufacturing process, such as the manufacturer of the diluents, the laboratory in charge of the finished product, or the company in charge of labelling and packaging, or that participates in any other stage of the process, in cases where they are not declared in the Certificate of Pharmaceutical Product, pursuant to the World Health Organization (WHO) Certification scheme on the quality of pharmaceutical products moving in international commerce (CPP), granted by the National Regulatory Authority (NRA). The certificate of Good Manufacturing Practices (GMP) should indicate the areas for which the manufacturing plant is authorized to operate.

d) For medicines that need to be reconstituted, the name, address, telephone number, fax number, and e-mail address of the manufacturer of the diluent must be provided, in the event that it is included in the medicine's final packaging.

1.4. Information on the medicine regulatory status in other countries, for imported products.

1.4.1. Certificate of Pharmaceutical Product (CPP): based on the model established in the WHO "Certification scheme on the quality of Pharmaceutical Products Moving in International Commerce (CPP)." It applies to the case of imported medicines, as it is the certificate issued by the National Regulatory Authority (NRA) issuing the health registration. This certificate also attests to the Good Manufacturing Practices (GMP) of the manufacturing laboratory(ies).

1.4.2. If the country is not a member of the WHO certification scheme, the following must be submitted:

a) Certificate of Free Sale (CFS).

b) Certificate of Good Manufacturing Practices (GMP).

c) Documentary evidence of the registration of the medicine in the country of origin (where the manufacturer is located) with its respective registration numbers and dates.

d) Documented evidence of the medicine's marketing in the country of origin.

1.4.3. Information on registration and marketing status in other countries with respective registration dates, especially in the countries members of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co- operation Scheme (jointly referred to as PIC/S).

1.5. Medicine's technical information.

1.5.1. Summary of Product Characteristics (SPC): a proposal for the Summary of Product Characteristics (SPC) must be submitted, according to Annex 1, including information in support of its content.

1.5.2. Labelling and package insert: the proposed text for the label on the primary container, secondary container, or external packaging, as well as the package insert that will contain the information indicated in Annex 2, must be included.

1.5.3. Samples of final marketing packaging: samples or, in their absence, duplicate projects or models of the following must be provided:

a) The primary and secondary packaging for all dosage forms of the medicine to be marketed.

b) The package insert.

c) Accessories, if applicable.

1.5.4 Samples of the finished product: two samples of the finished product in its original container, for each dosage form, if more than one, may be submitted for the respective evaluations.

1.6. Environmental risk assessment.

In the case of medicines such as hormones, antineoplastic agents, radiopharmaceuticals, among others, please include an assessment of any potential risks that their utilization or disposal may pose to the environment and living organisms, as well as any indications or warnings that should be included in the product insert, according the National Regulatory Authority (NRA).

Module 2: Quality Information

2.1. Module table of contents.

There will be a table of contents with all the documentation listed in this module.

2.2. Contents.

It includes information on the Active Pharmaceutical Ingredients (API), excipients (E), and finished product (FP), as indicated below:

2.2.1. Active Pharmaceutical Ingredients (API).

2.2.1.1. API. Nomenclature and properties of the Active Pharmaceutical Ingredients: the following must be submitted:

a) Name of the Active Pharmaceutical Ingredients (API) according to the International Non-proprietary Names System (INN) and the Anatomical Therapeutic Chemical Classification (ATC) System.

b) Chemical name, in accordance with WHO and Pharmacopeia monographs, as appropriate.

c) Chemical Abstract Service (CAS) or International Union of Pure and Applied Chemistry (IUPAC) registration number.

2.2.1.2. API. Chemical Structure and Molecular Formula: the following must be submitted:

a) Molecular formula.

b) Chemical structure formula, including absolute and relative stereo chemical formula.

c) Molecular weight and relative molecular mass.

2.2.1.3. API. Physicochemical characteristics: the following must be submitted:

a) Complete organoleptic and physical description, such as appearance, color, and physical state, as appropriate.

b) Solubility in relation to common solvents (water, alcohol, ether, acetone, chloroform).

c) Partition coefficient.

d) Distribution of particle size, if relevant.

e) Hygroscopic properties.

f) Polymorphism: indicate presence/absence of polymorphic or pseudo polymorphic forms (water/crystallization solvents), as specified in recognized pharmacopeia or international bibliography.

2.2.1.4. API. Mode of synthesis or process of obtaining for new API: a brief description of the synthesis or process of obtaining must be submitted, including:

a) All steps to obtain the API.

a.1. The list of components involved in the manufacturing process:

- Raw materials.
- Reagents, solvents, catalysts.
- Intermediate materials.

a.2. The list of equipment.

b) A flow chart of synthesis process for obtaining the API, including:

b.1. Identification of critical points.

b.2. Process controls and acceptance limits.

b.3. A list of operational parameters.

b.4. Controls of critical steps and intermediate products:

- Declaration for each identified critical step and its quality specifications.
- Information on quality specifications for intermediate products, if any.

b.5. Information on potential polymorphs and methods of analysis for their identification, when available.

b.6. Stereoisomer contents in proportions that, when present, may compromise the efficacy and safety of the medicine.

c) Process validation: information on validation studies and/or process assessment studies and assessment studies of the critical stages of the manufacturing process must be submitted (protocol, analysis of the results and conclusions).

d) For Active Pharmaceutical Ingredient (API) particles produced by fermentation, include: the type of microorganism and the composition of the environment, as well as any precursors and controls of reaction conditions.

e) For Active Pharmaceutical Ingredient (API) particles of vegetable origin, include the following information:

e.1. Description of its botanical classification, the part of the plant used, and how it is to be extracted.

e.2. Their geographical origin and the season during which they were collected (harvested).

e.3. The nature of chemical fertilizers, pesticides, fungicides, or other agricultural defensives used.

2.2.2. API. Control of the Active Pharmaceutical Ingredient (API).

2.2.2.1. API. Quality specifications: the following must be submitted:

a) A complete description of quality indexes or specifications (physical, chemical, and microbiological) and acceptance limits, including the quality reference (reference pharmacopeia or the manufacturer's own reference).

b) If the reference is the manufacturer's own, include any impurities resulting from the synthesis, their identification, and the rationale justifying the acceptance limits.

2.2.2.2. API. Methods of analysis: the following must be submitted:

a) A specific monograph, when it is from a reference pharmacopeia.

b) A full description of the method of analysis, when it is the manufacturer's own.

2.2.2.3. API. Validation of the method of analysis.

a) For products with specifications from a reference pharmacopeia, the following is required:

a.1. Information on the evaluation or feasibility study of the method performance, when fully applying the provisions contained in the analytical procedure of the pharmacopeia in question.

a.2. Information on the validation of any applicable parameters, when modifications are made to the provisions contained in the analytical procedure of the pharmacopeia in question.

b) In products with the manufacturer's own methods of analysis, it is essential to provide validation summaries that include experimental data on the characteristic parameters.

2.2.2.4. API. Certificates of analysis: a certificate of analysis from the original manufacturer must be included, with verification of its respective quality specifications, corresponding to the lots used in the product to be registered.

a) In the case of combinations, the information requested here must be provided individually for each Active Pharmaceutical Ingredient (API) of the medicine.

2.2.2.5. API. Stability: submit stability study demonstrating the shelf life given to the API, under the storage conditions and container-closure system proposed for:

a) A new API (new molecule).

b) A new salt, ester, isomers, complex or derivate.

2.2.3. E. Excipients: the following must be submitted:

a) Name, quality reference, and full description of the quality specifications (indexes and acceptance limits) for each excipient.

b) When not from a pharmacopeia, the method of analysis used to verify the quality specifications is required.

c) List of animal or human origin excipients and description of the viral safety guarantee and adventitious agents.

d) For excipients whose origin implies a risk of transmitting Bovine Spongiform Encephalopathy (BSE), supporting documents on non-transmission of BSE issued by the appropriate authority are required.

e) For excipients used for the first time in a pharmaceutical product or for a new route of administration, the following is required:

- Details on its manufacturing process, characterization, and quality control, if applicable.
- Toxicology information confirming its safety.

2.2.4. FP. Finished Product:

2.2.4.1. FP. Pharmaceutical development: provide information on the studies conducted to establish the dosage form, formulation, manufacturing process, and the container-closure system of the medicine to be marketed, including:

- Compatibility of the API with the excipients.
- Compatibility among new combinations of API.

2.2.4.2. FP. Finished product description and composition: a description of the finished product's qualitative and quantitative composition, by dosage unit and percent (weight or volume) must be included, detailing each component, Active Pharmaceutical Ingredient(s), preservatives, stabilizers, and excipients, as applicable, indicating the function of each.

a) The composition should be indicated in table format.

b) In the case of products that need to be reconstituted, such as lyophilized preparations and injection powders, a description of the diluents and the container-closure system used for the diluents must also be included.

c) When there is an increase of the Active Pharmaceutical Ingredient in relation to the quantity indicated in the labelling, this need to be stated, specifying the quantity and percentage by which it increases. It is necessary to provide justification for the causes or reasons behind this, as well as for the quantity.

d) When the Active Pharmaceutical Ingredient is in the form of a salt or hydrate, with dosage or strength referring to the base, it is necessary to indicate the equivalence with the base. Those cases where it is

not possible to indicate the equivalence due to the quantity of the salt or hydrate varying in function of the potency or value determined in every lot, are exempted.

2.2.4.3. FP: Manufacture of the finished product: the following must be submitted:

2.2.4.3.1. FP. Lot formula: the qualitative and quantitative formula for the production lot or batch, including a list of all the components, must be submitted.

2.2.4.3.2. FP. Description of the manufacturing process: The following must be submitted:

a) A description of the manufacturing process, including all steps or stages up to completion of the finished product, along with its packaging and labelling.

b) A flow chart of the process, including the stages of formulation, fill, lyophilisation (if applicable), labelling, and packaging, indicating the points at which material input occurs and indicating intermediate steps, critical points, and process controls.

c) Description of controls at critical steps or stages and key intermediate products.

d) In cases where more than one manufacturer is involved in the process, the flow chart should include the step(s) in which each of them participates.

e) Information on process validation.

f) Reprocesses, with justification and duly validated, whenever applicable.

2.2.4.4. FP. Control of the finished product.

2.2.4.4.1. FP. Quality specifications.

a) Provide a complete description of the quality indexes or specifications (physical, chemical, and microbiological) and acceptance limits in table format, independently of the methods of analysis and quality reference (reference pharmacopeia or manufacturer's own reference).

b) Justify any omission of quality indexes established in the reference pharmacopoeias for the product whose registration is being requested.

c) All controlled or modified release solid forms (tablets, capsules, suppositories) require time-release testing.

2.2.4.4.2. FP. Methods of analysis: provide information on the methods of analysis used for quality control:

- A specific monograph, when it is from a reference pharmacopeia.
- A complete description of the method of analysis, when it is the manufacturer's own.

2.2.4.4.3. FP. Validation of methods of analysis.

a) In products with a valid pharmacopeia specification, the following is required:
   - Information on the evaluation or standardization of the method performance, when fully applying the provisions contained in the analytical procedure of the pharmacopeia in question.
   - Information on the validation of any applicable parameters, when modifications are made to the provisions contained in the analytical procedure of the pharmacopeia in question.

b) In products with the manufacturer's own methods of analysis, it is essential to provide validation summaries that include experimental data on the characteristic parameters.

2.2.4.4.4. FP. Certificates of analysis: a certificate with evidence of the quality specifications issued by the manufacturer of the finished product must be included. In the case of initial production of products in development, it is acceptable for the tests to be conducted in pilot batches.

2.2.4.4.5. FP. Reference standards and materials: provide information on reference standards and/or materials used in finished product control tests.

2.2.4.5. FP. Description of the container-closure system used: provide a detailed description of the type and form of the container in which the finished product will be packaged and its closure system, including name, quality reference, the materials they are made of, and quality specifications (index and acceptance limits) for each one.

2.2.4.6. FP. Stability studies of the finished product: submit stability study, according to the appropriate climate zone.

2.2.4.6.1. FP. Protocols and results of the stability study that justify the proposed shelf life: submit the stability study, including the following:

a) Study protocol.

b) Quality specifications and methods of analysis.

c) Detailed description of the container-closure system used with the product being evaluated.

d) Storage conditions (temperature, light sensitivity and relative humidity in the environment).

e) Results from at least three lots of the finished product made using preferably different lots of the Active Pharmaceutical Ingredient.

f) Conclusions and proposed shelf life and storage conditions.

g) The stability studies must be signed off by the professional responsible for the study.

h) When the dosage form of the medicine is accompanied by a solvent or diluent, stability studies on the diluted, dissolved, or dispersed product, as applicable, under conditions of use, must be submitted.

i) If more than one vehicle is used for its preparation, data from the stability studies conducted for each of them must be submitted.

j) If a product is packaged in two to more container-closure systems, stability studies for each of them must be submitted.

k) If a product is packaged in two or more volumes, stability studies according to the international regulations in force must be submitted.

l) Accelerated and therapeutic life (shelf-life) studies or shelf-life only studies must be submitted.

2.2.4.6.2. FP. Post-marketing authorization stability studies programme: include the stability program to be implemented or stability commitment to be maintained during the marketing stage of the finished product, including the number of lots to incorporate into the study each year and the analyses to be conducted. These results shall be submitted periodically to update the information on product stability. The following cases require the submission of shelf-life studies (long term), made only with approved industrial lots and under approved storage and container-closure system conditions:

a) To confirm or extend the provisional shelf life approved in the registration, when the results of accelerated stability studies and shelf life studies submitted for registration, were obtained using pilot lots.

b) To confirm or extend the shelf life approved in the registration when the results of the shelf life studies submitted for registration did not cover such period.

2.2.4.6.3. FP. Description of the procedures used to guarantee the cold chain: in the case of products requiring refrigeration, provide a detailed written description of the measures adopted to guarantee proper temperature and humidity conditions for transporting the finished product from the production site to the final point of sale, including all stages of storage and distribution and indicating the controls performed at each stage. It should also indicate extreme temperature conditions not covered by recognized international standards, if applicable. This description must be signed by the responsible professional.

2.2.4.7. FP. Biopharmaceutical documentation: according to the "Framework for Implementation of Equivalence Requirements for Pharmaceutical Products" prepared by the Bioequivalence Working Group and approved by the Fifth Pan American Network on Drug Regulatory Harmonization (PANDRH) Conference, according to the decision tree criteria for bioequivalence studies, the following may be required:

a) Dissolution test (for dosage forms that require it).

b) In vitro equivalence studies (dissolution profile).

c) In vivo equivalence studies.

Module 3: Nonclinical Reports

3.1. Module table of contents.

There will be a table of contents with all the documentation listed in this module.

3.2. Nonclinical Trials.

3.2.1. For new Active Pharmaceutical Ingredients (API).

3.2.1.1. Pharmacodynamic studies.

3.2.1.2. Pharmacokinetic studies.

3.2.1.3. Toxicology. The following information must be submitted:

a) General toxicology:

- Study design and justification of the animal model.
- Animal species used, age, and size of the groups.
- Doses, route of administration, duration of the studies, and control groups.
- Monitored parameters.
- Local tolerance.

b) Special Toxicology:

- Special immunological research.
- Toxicity studies in special populations.
- Genotoxicity and carcinogenicity studies: when applicable.
- Reproductive toxicity studies: for medicines to be administered in pregnant women or individuals in reproductive age.

3.2.2. For new combinations: provide the respective pharmacodynamic studies.

3.2.3. For new substances added to the formulation, new stabilizers or additives, the respective toxicology studies must be provided.

Module 4: Clinical Reports

4.1. Module table of contents.

There will be a table of contents with all the documentation listed in this module.

4.2. Clinical trials.

4.2.1. Clinical trials for new API.

4.2.1.1. Summary of the clinical trials conducted.

4.2.1.2. Phase I studies. These are primarily aimed at defining the safety, pharmacokinetics and bioavailability of the product in the case of medicines with new APIs.

a) Include in the pharmacokinetics aspects, the results of comparative studies in healthy volunteer subjects, special patients and population; related to intrinsic factors (age, sex, ethnicity, kidney or hepatic failure) and extrinsic factors (smokers, concomitant medicines, diet); absorption data; distribution (plasma protein binding); metabolism (specific metabolic route, effects of potential genetic polymorphism, and active and inactive metabolite formation); excretion; medicine interaction with other clinically relevant products or substances.

b) Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects. Medicines with significant potential toxicity, such as cytotoxic medicines, are usually studied in patients. Studies in this phase can be open, baseline controlled, or may use double-bind randomization to improve the validity of the observations.

4.2.1.3. Phase II studies. For medicines based on new Active Pharmaceutical Ingredients (APIs):

a) These studies are conducted after the conclusion of the Phase I studies to explore the therapeutic efficacy in patients using the drugs for a particular indication or indications in patients with a disease or condition. Initial clinical exploratory studies may use a variety of designs, including controls and comparisons with a baseline.

b) Subsequent clinical studies are usually randomized and controlled at the same time to evaluate the efficacy and safety of the medicine, especially the therapeutic indication. An important goal for this phase is to determine the dose(s) and regimen for Phase III trials.

c) Early studies in this phase often utilize dose escalation designs to obtain an initial dose-response estimate, and later studies may confirm the dose-response relationship for the indication in question by

using recognized parallel dose-response designs (it could also be deferred to Phase III). Confirmatory dose-response studies may be conducted in Phase II or left for Phase III. Doses used in Phase II are usually, but not always, less than the highest doses used in Phase I.

d) Additional objectives of clinical trials conducted in Phase II may include an evaluation of potential study endpoints, therapeutic regimes (including concomitant medications) and target population (e.g. a mild versus a severe disease) for further study in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in the trials.

4.2.1.4. Phase III studies: for medicines made based on new molecules or APIs:

a) Studies in Phase III have been designed to confirm the preliminary evidence accumulated in Phase II that a medicine is safe and effective for use in the intended indication and target population. These studies are intended to provide an adequate basis for marketing approval.

b) These are large-scale studies designed to provide medicine efficacy and safety data. These studies can recruit several thousand subjects (this will be defined by the study's endpoint).

c) Studies in Phase III may also further explore the dose-response relationship, or explore the medicine's use in wider populations, at different stages of disease, or in combination with other medicine.

d) Studies carried out in Phase III complete the information necessary to support adequate instructions for medicine use (summary of product characteristics).

e) Information on the medicine's safety profile, including utilization outcomes, not only in short-term treatments, but also in long-term treatments (more than a month) must be provided, especially in the case of medicines indicated for chronic diseases.

4.2.1.5. Phase IV studies—pharmacovigilance plan: when applicable, depending on the type of medicine, the protocol from Phase IV studies or the results of studies already conducted may be requested.

4.2.1.6. Studies on special populations: when applicable, according to the medicine's indications.

4.2.2. Clinical trials for known APIs: these are studies submitted with each new API combination; salt, ester, isomer, complex or derivative; dosage form and route of administration; or strength not included in the currently registered dosage range, and not characterized as a pharmaceutical alternative.

a) The NRAs define the types of studies required for these cases, taking into account the guidelines and documents issued by the WHO and PANDRH.

b) In the case of new combinations, the recommendations from WHO Technical Report Nº 929, Annex 5, 2005 or its updates shall apply.

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Annex 1:
Summary of Product Characteristics (SPC)

1. Summary of Product Characteristics (SPC).

   The SPC contains medicine information prepared by the respective National Regulatory Authority, once the medicine has been evaluated and approved for marketing. The SPC is publicly accessible and geared primarily to ward health professionals to ensure that the medicine will be prescribed, dispensed, and used rationally, safely, and effectively.

2. Content of the SPC.

   The information that the applicant requesting the registration of the medicine must submit, so that the respective national medicine regulatory authority can prepare the SPC, is the following:

   a) Product name (brand name).
   b) International Non-Proprietary Name (INN) (generic name).
   c) Dosage form.
   d) Strength.
   e) Packaging.
   f) Manufacturer and address of the manufacturing site.
   g) Composition in terms of active pharmaceutical ingredients and excipients that could cause undesirable effects.
   h) Shelf life.
   i) Storage conditions.
   j) Therapeutic indications.
   k) Contraindications.
   l) Precautions.
   m) Warnings.
   n) Use during pregnancy and breast-feeding.
   o) Effects when operating vehicles/machinery.
   p) Interactions with other pharmaceutical products as well as other forms of interaction.
   q) Undesirable effects.
   r) Dosage, according to age, way of using and route of administration.
   s) Instructions for use, handling, and destruction of any unusable remainder of the product.
   t) Overdose.
   u) Pharmacodynamic properties.

v) Pharmacokinetic properties (absorption, distribution, biotransformation, elimination).

w) Anatomical Therapeutic Chemical Classification (ATC) Code.

3. Format.

   This information should be submitted in electronic format using a text processor that allows for modifications.

Annex 2:
Labelling and Package Insert

1. Labelling and package insert information.

   The proposed text for labelling the primary container, secondary container, or exterior packaging, as well as the package insert should be included.

   1.1. Label on the primary container.

   Submit the proposed label for the primary container, which should contain at least the following information:

   a) Brand name.

   b) International Non-Proprietary Name (INN) (generic name).

   c) Dosage form (whenever this is a dosage form with an unconventional type of release, it should be mentioned).

   d) Concentration of the API by dose or volume.

   e) Contents/volume (for commercial packing).

   f) Volume/dose to be administered, if applicable.

   g) Route of administration.

   h) Number of doses per container (for multidosis packaging), when applicable.

   i) Conditions of storage (if the size of the container permits it).

   j) Warnings (if the size of the container permits it).

   k) Lot number.

   l) Expiration date.

   m) Name (or logo) of the marketing authorization holder or manufacturer.

   n) Registration number (if the size of the container permits it).

   1.2. Label on the secondary container.

   Include the proposed labelling text for the secondary container, also called the package, that protects the container in which the medicine is kept; this should indicate at the very least the information indicated below:

   a) Brand name.

   b) International Non-Proprietary Name (INN) - generic name.

   c) Dosage form.

   d) Route of administration.

e) Concentration.

f) Contents/volume.

g) Number of doses per container (for multidosis packaging), when applicable.

h) Composition.

i) Dispensing/sale conditions.

j) Declaration of excipients.

k) Conditions for product storage (indicate sensitivity to light, where applicable).

l) Instructions for preparation (if applicable).

m) Instructions for use.

n) Warnings (if applicable).

o) Distinctive characteristics for identification/authenticity, if applicable.

p) Lot number.

q) Expiration date.

r) Name of the manufacturer of the finished product and address of the manufacturing site.

s) Name and address of the packager.

t) Name and address of the marketing authorization holder, representative, or distributor (should include city of domicile and country).

u) Name of the responsible professional.

v) Registration number.

1.2.1. Special warnings: It has to include special warnings to ensure the adequate use of the medicine, when applicable.

1.2.2. The use of drawings or pictures in the package is forbidden. At the same way, no claims or attributes can be claimed associated with the authorized indication, nor any other related to the medicines for sale over the counter (OTC).

1.3. Package insert.

Include the proposed text for the package insert, which should contain the information indicated below at the very least, in patient friendly language:

a) International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical Classification (ATC).

b) Brand name.

c) Dosage form.

d) Concentration.

e) Contents/volume.

f) Number of doses per container (for multidosis packaging), when applicable.

g) Composition.

h) Declaration of excipients.

i) Route of administration.

j) Indications (resulting from clinical trials that assess the medicine's efficacy).

k) Instructions for use.

l) Posology/dosage.

m) Maximum dose in 24 hours, for over-the-counter (OTC) products.

n) Precautions.

o) Warnings.

p) Adverse reactions.

q) Contraindications.

r) Interactions.

s) Overdose (risk and information on how to manage risk).

t) Use during pregnancy and breast-feeding.

u) The importance of monitoring patient use and where to report possible problems with the medicine.

v) Product storage/storage conditions.

w) Name and address of the marketing authorization holder.

x) Name and address of the manufacturer of the finished product.

y) Name and address of the packager.

z) Conditions for dispensing/sale.

ISBN 978-92-75-11757-6

PANDRH Series - Technical Document No. 10

Requirements for Medicines Registration in the Americas