PAN AMERICAN NETWORK FOR
DRUG REGULATORY HARMONIZATION (PANDRH)

WORKING GROUP ON MEDICINES REGISTRATION

GUIDELINES FOR MEDICINES REGISTRATION IN THE AMERICAS (DRAFT – MAY, 2011)

Introduction

1. This document is a proposal for guidelines for medicines registration in the Region of the Americas, prepared by the Working Group on Medicines Registration of the Pan American Network on Drug Regulatory Harmonization (PANDRH).

2. National standards will be set in keeping with each country's legislation. The presentation of the information should be in the language of the country where the medicines are being registered.

3. These guidelines will be applicable to the following types of medicines:

a) Active Pharmaceutical Ingredient (API) with know dosage form;
b) Active Pharmaceutical Ingredient of known use presented with a new:
- Association 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.

4. These guidelines 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.

5. It recommends the establishment of a valid registration period of five years and its renewal for the same period of time. The National Regulatory Authority (NRA) may withdraw the product if there is a loss of effectiveness, safety or quality issues, according to health risk criteria. Changes in registration must be notified and authorized by the NRA.

6. These guidelines follow those found in other similar documents on the Pan American Network on *Drug Regulatory Harmonization (PANDRH) and it* consists of four (4) modules and two (2) annexes.

Module 1: Administrative and Legal Information;
Module 2: Quality Information;
Module 3: Non-clinical 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 for medicines registration, pursuant to its legislation. The registration application form should contain at least 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 Characteristics of the Medicine

1.2.1 **Name(s) of the Active Pharmaceutical Ingredient(s) (IPA):** There should be an indication according to the International Non-proprietary Names System (INN) and the Anatomical Therapeutic Chemical Classification System (ATC).

1.2.2 **Brand Name:** The name under which the medicine will be marketed, if applicable.

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 posological unit.

1.2.4 **Dosage Form:** Indicate the type of preparation, for example: injectable solution, lyophilized powder for injectable suspension.

1.2.5 **Route of Administration:** Specify the route of administration.

1.2.6 **Medicine Presentation:** State the content or amount of the medicine and the type of primary and secondary package (container closing system), whether to distribute in a single-unit or multi-unit package, as well as the conditions that are for dispensing. Any additional accessory—for example, a transfer device—needs indication.

1.2.7 **Description and Interpretation of the Batch Code:** means any combination of letters or figures, or both, to trace any medicine, in manufacture and identified in distribution.

1.2.8 **Expiration date:** The expiration date cannot appear in coded form, as this might prevent its proper interpretation.

1.2.9 ***Dispensing Condition:*** 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 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** of the non-reconstituted or reconstituted product, as appropriate.

1.3 Legal Documentation

The legal information duly certified by the respective entity.

1.3.1 **Technical Director/Health Agent in Charge:** This is the technical professional assigned responsibility in the country where there is the registration of the medicine. This should include:

a) The document issued by the owner of the medicine, clearly indicating all the data on the professional named as technical director, who will be the technical expert responsible for the product in that country. It should state his/her name, address, telephone, fax, e-mail, registration number of the professional council with which she/he is affiliated, and the number of his/her academic degree.

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

1.3.2 **Marketing authorization holder:** State the full name of the marketing authorization holder or owner of the medicine, providing the complete address, telephone, fax, and e-mail.

a) Provide a document or written communication showing the business name of the market authorization holder that accredits the legal representative to the respective national medicine regulatory authority.

b) There should be the submission of the information when the marketing authorization holder requests the registration of a medicine for the first time; it is not necessary to submit it for each subsequent change request to the registered medicine. This information requires updating whenever the medicine undergoes any modifications.

1.3.3 **Legal Representative in the Country:** This refers to the company that represents the product and will be in charge of its registration and/or marketing in the country. Provide the full name, address, telephone, fax, and e-mail.

a) Must have a document or written communication issued by the marketing

authorization holder or owner of the medicine, authorizing the company or institution to represent it and empowering it to submit applications for registering and marketing the authorized products (when applicable).

b) The submission of the information when the marketing authorization holder requests the registration of a medicine for the first time; it is not necessary to submit it for each subsequent change request to the registered medicine. The update of information whenever the medicine undergoes any modifications.

1.3.4 **Manufacturer of the Active Pharmaceutical Ingredients(s):** Indicate the name(s), address, telephone, fax, and e-mail of the laboratory or laboratories that manufacture the Active Pharmaceutical Ingredient(s) (when applicable or when the country includes it in its legislation).

1.3.5 **Manufacturer of the Finished Product:** Indicate the name(s), address, telephone, fax, and e-mail of the laboratory or laboratories that manufacture the final product and submit the following information and documents:

a) In cases where there is more than one, 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 marketing authorization holder or owner, the legal document should indicate the relationship between the two.

c) Certificate of Good Manufacturing Practices (GMP) from the manufacturer(s) involved in the medicine manufacturing process: for example, the manufacturer of the diluents', or the laboratory in charge of the finished product and its labelling or packaging or that participates in any other stage of the process, in cases not declared in the Certificate of a Pharmaceutical Product (CPP), pursuant to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. The Certificate of Good Manufacturing Practices should indicate the areas in which the manufacturing plant is authorized to operate.

d) For medicines that need to be reconstituted, provide the name, address, telephone, fax, and e-mail of the manufacturer of the diluents, in the event that it is included in the medicine's final presentation.

1.4 Information on the Regulatory Situation of the Medicine in Other Countries, for Imported Products

1.4.1 **Registration in the Country of Origin (where the manufacturer is located):** Indicate whether there is the registration of the medicine in the country of origin with its respective registration numbers and dates. State whether there is marketing of the medicine in the country of origin.

1.4.2 **Certificate of a 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 Regulatory Authority that issues the registration. This certificate also attests to the Good Manufacturing Practices of the manufacturing laboratory(ies). If the country is not a member of the WHO certification scheme, show the Certificate of Free Sale (CFS) and the Certificate of Good Manufacturing Practices (GMP).

1.5 Technical Information on the Medicine

1.5.1 **Summary of Product Characteristics (SPC)**: Submit information for preparing the summary of the characteristics (SPC) of the medicine evaluated, as indicated in Annex 1.

1.5.2 **Labelling and Package Insert:** Include 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.

1.5.3 **Monograph for Health Professionals:** Submit the proposed monograph on the medicine that will be distributed to health professionals, if applicable.

1.5.4 **Samples of Final Marketing Packaging:** Submit samples or, in their absence, duplicate projects or models of:

a) The primary and secondary packaging for all forms of the medicine to be marketed;
b) The package insert;
c) Accessories, if applicable.

1.5.5 **Samples of the Finished Product:** Pursuant to the country's legislation, for the respective evaluations, submit two samples of the finished product in its original container, with samples of each form where there is more than one.

1.6 Environmental Risk Assessment

In the case of medicines such as hormones and antineoplastic medicines, radioactive, among others, include an assessment of any potential risks to their utilization or elimination in the environment and living things, as well as any indications or warnings that should be included in the product labelling.

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

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

2.2.1. ACTIVE PHARMACEUTICAL INGREDIENTS (API)

2.2.1.1. Nomenclature and Properties of the Active Pharmaceutical Ingredient:

a) Name of the Active Pharmaceutical Ingredient according to the International Non-proprietary Names System (INN) and the Anatomical Therapeutic Classification System (ATC);
b) Chemical name, in accordance with WHO and Pharmacopeia monographs, as appropriate;
c) Chemical Abstract Service (CAS) or IUPAC registration number.

2.2.1.2. Chemical Structure and Molecular Formula:

a) Molecular formula;
b) Formula of its chemical structure, with the absolute and relative stereo chemical formula;
c) Molecular weight and relative molecular mass.

2.2.1.3. Physicochemical Characteristics:

a) Complete organoleptic and physical description, e.g. appearance, colour, 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. Mode of Synthesis or Process of Obtaining for new API:

a) Submit a brief description of the synthesis or process of obtaining, including:
    a.1 All steps to obtain the API;
    a.2 The list of components involved in the manufacturing process:
        - Raw materials;

- Reagents, solvents, catalysts;
- Intermediate materials.

a.3 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 Value of operational parameters;

b.4 Controls of Critical Steps and Intermediates:

- Declaration for each identified critical stage and its quality specifications;
- Information on the quality specifications of the intermediate products, if any.

c) Validation of the process. Information on the validation studies and/or assessment processes and critical stages of the manufacturing process has to be presented (protocol, analysis of the results and conclusions).

d) For Active Pharmaceutical Ingredient 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 particles of vegetable origin, include the following information:

- Description of its botanical classification, the part of the plant used, and how it is to extracted;
- Their geographical origin and the season during which they were collected (harvested);
- The type of chemical fertilizers, pesticides, fungicides, or other agricultural defences used.

2.2.2. API: CONTROL OF THE ACTIVE PHARMACEUTICAL INGREDIENT

2.2.2.1. API: Quality Specifications

a) Provide a complete description of quality indexes (physical, chemical, and microbiological) and acceptable limits, with the quality reference (pharmacopeia or from the manufacturer);

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

2.2.2.2. API: Methods of Analysis

a) A specific monograph, when from a pharmacopeia;

b) A complete description of the method of analysis, when from the manufacturer.

2.2.2.3. API: Validation of the Method of Analysis

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

- Information on the evaluation or standardization of the application of the method, when the provisions in the analysis procedure of the pharmacopeia in questions are fully applied;
- Information on the validation of any corresponding parameters, when modifications made to the provisions in the analysis procedure of the pharmacopeia in question.

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

2.2.2.4. ***API: Certificates of Analysis****:* Include a certificate of analysis from the original manufacturer, with verification of its respective quality specifications. *Note:* In the case of associations, the information requested here ***should be provided individually for each Active Pharmaceutical Ingredient*** of the medicine.

2.2.3. E: EXCIPIENTS

a) Name, quality reference, and complete description of the quality specifications (indexes and acceptable 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 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 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 closing system of the medicine to be marketed:
- Compatibility of API with the excipients;
- Compatibility among new combinations of API.

2.2.4.2. ***FP: Finished Product Description and Composition:*** Include a description of its qualitative and quantitative composition, by dosage unit and percent (weight or volume), detailing each component, Active Pharmaceutical Ingredient(s), preservatives, stabilizers, and excipients, whenever 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, also include a description of the diluents and the container closing system used for the diluents;
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. 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, indicate the equivalence with the base. Cases where it is not possible to describe the equivalence will be exempt, since the quantity of the salt or hydrate varies with the potency or value determined in every lot.

2.2.4.3. FP: Manufacture of the Finished Product

2.2.4.3.1. ***FP: LOT FORMULA*** Provide the formula for the production lot, including a list of all the components.

2.2.4.3.2. FP: DESCRIPTION OF THE MANUFACTURING PROCESS

a) A narrative of the manufacturing process that includes all steps or stages up to completion of the finished product, along with its packaging and labelling;
b) A flow chart of this process that includes 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 controls in this process;
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 (physical, chemical, and microbiological) and acceptable limits in table format, independently of the methods of analysis and quality reference (pharmacopeia or manufacturer);
b) Justify any omission of the quality indexes established in the pharmacopoeias for the product whose registration is being requested;

c) All solid forms of controlled or modified release (tablets, capsules, ovules) 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 from a pharmacopeia;
- A complete description of the method of analysis, when from the manufacturer.

2.2.4.4.3. FP: VALIDATION OF METHODS OF ANALYSIS

a) In products with pharmacopeia specification, the following is required:
   - Information on the evaluation or standardization of method performance, when the provisions in the method of analysis of the pharmacopeia in question are fully applied;
   - Information on the validation of the respective parameters, when modifications are made to the provisions in the method of analysis of the pharmacopeia in question;

b) In products with methods of analysis from the manufacturer, it is essential to provide summaries of the validation that reflect the experimental data of the characteristic parameters.

2.2.4.4.4. FP: CERTIFICATES OF ANALYSIS: Include a certificate verifying the quality specifications issued by the manufacturer of the finished product.

2.2.4.4. FP. REFERENCE STANDARDS AND MATERIALS: Provide information on the reference standards and/or materials used in the tests to monitor the finished product.

2.2.4.5. FP: Description of the Container Closing System Used for the Finished Product: Provide a detailed description of the type and form of the container in which the finished product will be packaged and the closing system, including the materials they are made of and quality specifications.

2.2.4.6. *FP: Stability Studies on the Finished Product:* Submit stability Study, according to the respective climate zone.

2.2.4.6.1. ***FP: PROTOCOLS AND RESULTS OF THE STABILITY STUDY THAT JUSTIFY THE PROPOSED EXPIRATION*** Submit the stability study, including the following:

a) Study protocol;
b) Quality specifications and methods of analysis;
c) Detailed description of the container closing system used with the product being evaluated;
d) Storage conditions (temperature and relative humidity in the environment);
e) Results from at least three lots of the finished product (using preferably different lots of the Active Pharmaceutical Ingredient);
f) Conclusions and proposed expiration date and storage conditions;

g) The professional responsible for the study should sign off on the stability studies;
h) When the dosage form of the medicine is accompanied by a solvent or diluents, include stability studies on the diluted, dissolved, or dispersed product, as applicable, in the conditions under which it is to be utilized;
i) If more than one vehicle is used for its preparation, submit data from the stability studies conducted for each of them;
j) If a product is packaged in two to more container closing systems, present the stability studies for each of them.

2.2.5.6.2. ***FP: STABILITY PROGRAM ONCE THE MARKETING AUTHORIZATION HAS BEEN ISSUED:*** Include the stability program to be implemented or the Stability Commitment to be maintained during the marketing stage of the finished product, including the lot number to incorporate annually into the study and the analyses to be conducted. These results will be submitted periodically to update the information on product stability.

2.2.5.6.3. ***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. This description should be signed by the professional in charge.

2.2.4.7. FP: Biopharmaceutical Documentation: According to the *Framework for Compliance with Equivalence Requirements for Pharmaceutical Products* prepared by the Bioethics Working Group and approved by the Fifth Conference, 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: Non-clinical Reports

3.1 Module Table of Contents

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

3.2. Non-clinical Trials

3.2.1. For New Active Pharmaceutical Ingredient

3.2.1.1. Pharmacodynamics 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;
- Dose, route of administration and control groups;
- Monitored parameters;
- Local tolerance.

b) Special Toxicology

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

3.2.2. For New Associations: Provide the respective pharmacodynamics studies.

3.2.3. For New substances added to the Formulation (new stabilizers, additives), other routes of administration, and new associations, provide the respective toxicology studies.

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 based on* ***new API.***

4.2.1.3. Phase II Studies

For Medicines Based on new API. These studies are conducted after the conclusion of the Phase I studies. The main distinction between Phases I and II is that the Phase II studies involve a sizable number of subjects and are usually controlled and randomized. The Phase II studies should define the optimal dosage and, very importantly, the medicine's safety before starting Phase III.

4.2.1.4. Phase III Studies: These are large-scale studies designed to deliver data on the efficacy and safety of the medicine. In these studies, several thousand subjects can be recruited (this will be defined by the "end point" of the study).

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 indications.

4.2.2. Clinical trials for new strength, new pharmaceutical form, new indication or new combination of known APIs

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

- In the case of new associations, it is applicable the recommendations from the Technical Report Nº 929, Anexo 5, de la OMS, 2005.

Annex 1

1. Summary of Product Characteristics (SPC)

The SPC contains 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 health professionals to ensure that the medicine will be prescribed, dispensed, and used rationally, safely, and effectively.

2. The following information should be submitted by the applicant requesting the registration of the medicine, so that the respective national medicine regulatory authority can prepare the SPC:

a) Product name (brand and generic name);
b) Dosage form;
c) Strength;
d) Presentation;
e) Manufacturer and country;
f) Composition in terms of active pharmaceutical ingredients and excipients that can cause undesirable effects;
g) Expiration date;
h) Storage conditions;
i) Therapeutic indications;
j) Contraindications;
k) Precautions;
l) Warnings;
m) Use during pregnancy and breast-feeding;
n) Effects when operating vehicles/machinery;
o) Interactions with other medicinal products as well as other forms of interaction;
p) Undesirable effects;
q) Dosage and route of administration;
r) Instructions for use, handling, and destruction of any unusable remainder of the product;
s) Overdose;
t) Pharmacodynamic properties;
u) Pharmacokinetic properties (absorption, distribution, biotransformation, elimination).

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

Annex 2

1. Labelling and Package Insert

Include the texts proposed for labelling the primary container, secondary container, or exterior packaging, as well as the package insert.

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) Generic name;
c) Dosage form (whenever this is a dosage form with an unconventional type of release, it should be mentioned);
d) Route of administration (if applicable);
e) Concentration/composition;
f) Contents/volume;
g) Volume/dose;
h) Number of doses per container (for multidose presentation);
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) Generic name;
c) Dosage form;
d) Route of administration;
e) Concentration;
f) Contents/volume;
g) Number of doses per container (for multidose presentation);
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) Distribution level;

p) Distinctive characteristics for identification/authentication, if applicable;
q) Lot number;
r) Expiration date;
s) Name and address of the manufacturer of the finished product;
t) Name and address of the packager;
u) Name and address of the marketing authorization holder, representative, or distributor (should include city of domicile and country);
v) Name of the professional in charge;
w) Registration number.

1.3. Package Insert

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

a) International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical Classification (ATC);
b) Patent name;
c) Dosage form;
d) Concentration;
e) Contents/volume;
f) Number of doses per container (for multidose presentation);
g) Composition;
h) Declaration of excipients;
i) Route of administration;
j) Indications;
k) Instructions for use;
l) Posology/dosage;
m) Maximum dose in 24 hours, for over-the-counter 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 manufacturer of the finished product;
x) Name and address of the packager;
y) Conditions for dispensing/sale.

Glossary

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).

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.

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.

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

Lot (batch): A quantity of raw material, packaging material, or product manufactured in a process or series of processes in a way that is uniform. 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 sub-lots, 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.

Known Medicines: See Pharmaceutical Equivalent.

Shelf Life (also known as expiration date): Period within which the medicine is expected to maintain its quality specifications as established in the marketing authorization, if stored according to the manufacturer's recommendations, as demonstrated in the stability studies conducted.

Active Pharmaceutical Ingredient: 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.

Product to Register: The medicine to be registered.

Biological: 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 components or by products, 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.

Final bulk: Every product that has gone through all stages of processing 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.

Sanitary Registration: This is the procedure whereby the national regulatory authority grants authorization for the nationwide marketing and distribution of the product in question, pursuant to the country's legislation.

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.

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.

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