PAN AMERICAN NETWORK ON DRUG REGULATORY HARMONIZATION

WORKING GROUP ON REGISTRATION OF MEDICINES

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PAN AMERICAN NETWORK FOR DRUG REGULATORY HARMONIZATION (PARF NETWORK)

WORKING GROUP ON DRUG REGISTRATION

PROPOSAL OF HARMONIZED REQUIREMENTS FOR DRUG REGISTRATION IN THE AMERICAS

Introduction

This document is a proposal of harmonized minimum requirements for Drug Registration in the Americas Region, prepared by the Working Group on Drug Registration from the Pan American Network for Drug Regulatory Harmonization, considering the type of drug: new molecule, new strength, association or formulation or known product.

Each country has an application form of the sanitary certificate, complying with its legislation. Said form should contain at least the following information:

1. **Trademark Name :** It is a registered trademark used to commercialize the drug, if applicable.

2. **Generic name:** According to international common denomination (ICD) and the Therapeutic Class Code (TCC).

3. **Strength:** Strength of the active ingredient(s) contained in the drug should be stated.

4. **Pharmaceutical Form:** It should indicate the pharmaceutical form, for example: injection solution, frozen dried power for suspension for injection.

5. **Technical Director/Sanitary Responsible:** It is the health responsible person for the product in the country where drug registration is required and the person in charge of filing the procedure before the corresponding National Drug Regulatory Authority (DRA). In some countries it is called Responsible Officer. There are cases where this sanitary officer is responsible also for the production and quality control at the manufacturer's plant and some countries may designate said person as Pharmacist in Charge (PIC) to differentiate him from the officer who is only responsible for the product before the Regulatory Authority.

   He should state his Name, Address, Phone Number, Fax, Electronic Mail, and Registration Number of the Professional Health Association where he is registered with and professional title registration number according to the country's legislation.

6. **Legal Representative in country:** It refers to the Company that represents the product and that is in charge of its marketing in country. Complete name, address, phone number, Fax and Electronic mail should be stated. Some countries in the region do not require a Legal Representative for drug registration of a product.

7. **Holder of Drug at international level:** the complete name of the drug holder Address, Phone number, Fax and electronic mail should be stated.

8. **Manufacturer of Active ingredient(s):** It should indicate the Name(s), Address, Phone number, Fax, electronic mail, of the manufacturer(s) of the active ingredient (s).(If a country's legislation so stipulates it)

9. **Final product manufacturer:** It should indicate the Name (s), Address, Phone number, Fax, electronic mail of the laboratories that manufacture the final product(s).

10. **Other laboratories participating in the manufacturing process:** In case that any part of the process is performed by other laboratory, Name, Address, Phone number, fax, electronic mail thereof should be stated.
For freeze dried drugs Name, Address, Phone number, Fax, electronic mail of the diluent's manufacturer should be stated.

11. **Commercial Drug Package:** Regardless if the product shall be distributed in one dose and several doses in the same package and if it contains an additional accessory, for example a transfer device.

12. **Route of Administration:** It should state the route of administration indicated.

13. **Storage conditions:** It should indicate the adequate storage temperature for the product.

14. **Dispensing condition**: According the country's legislation it should indicate whether dispensing requires facultative prescription.

15. **Quali-quantitative Posology and Percentage unit:** It should specify the product formula in terms of dosage unit and in percentage (%)**.**

16. **Legal Documents of the Product:** The legal information should be dully certified by the corresponding institution.

    - **Document endorsing the technical director/technical officer of the product** (according to the country's legislation): Document granted by the drug holder where he should clearly indicate all the officer information who shall be responsible for the product in country and who is authorized to perform the relevant regulatory activities, among which the drug registration.

- **Representative's Authorization:** Document granted by the drug holder, where he authorizes the Company to represent and market said product in country (when applicable)

- **Certificate of Pharmaceutical Product (CPP):** According to WHO models. Applicable in the case of imported drugs, it is the certificate issued by the Drug Regulatory Authority that grants the Drug Registration.

  This Certificate includes the Good Manufacturing Practices of the manufacturing lab. Some countries still issue the Free Sale Certificate (FSC) in which case it should also include the Good Manufacturing Practices Certificate.

- **Good Manufacturing Practices Certificate of the laboratories that participate in the drug production process, as** for example the diluent's manufacturer, the laboratory that conditions the final product, in charge of labeling and packaging or those demanded in any other stage of the process.

  The Good Manufacturing Practices Certificate (GMP) should indicate the procedures for which the establishment is authorized.

  Trade Mark Certificate (Optional)

17. **Summary of product characteristics:** a summary of the characteristics of the drug under review should be submitted.

18. **Labeling and Leaflet** : It should include the proposed text to condition the primary container, secondary container and external packaging, as well as the leaflet

19. **Label Primary Package l** To submit the labeling project for the primary container, which should contain at least the following information:
    - Commercial Name
    - Generic Name
    - Dosage Form
    - Strength
    - Content/volume
    - Volume/dosage
    - Number of doses per vial (for multi-doses presentation)
    - Route
    - Storage temperature (if the container size allows it)
    - Warnings
    - Batch Number
    - Expiration date
    - Manufacturer
    - Registration number (according to the country's legislation and if the container size so allows it).

20. **Secondary package container label:** To include in the proposed labeling text for the secondary container, also called package that protects the container containing the drug, which should at least have the following information.
    a. Commercial Name
    b. Generic Name
    c. Pharmaceutical form
    d. Strength
    e. Contents / volume
    f. Number of doses (for multi doses presentation)
    g. Composition
    h. Excipients statement (according the each country's legislation)
    i. Storage of the product
    j. Route
    k. Instructions for preparation
    l. Method of use
    m. Warnings (if container size allows it)
    n. Distribution level (according to each country's legislation)
    o. Identification features (according to the country's legislation). Some countries may request inclusion of some distinctive mark of the type of product, like for example, yellow band for pediatric use products.
    p. Batch number
    q. Expiration date
    r. Name and address of final product manufacturer
    s. Name and address of conditioner
    t. Name of Holder, Representative or Distributor and address (according to the country's legislation)
    u. Name of Responsible Officer (according to the country's Legislation)
    v. Registration number (according to the country's)

21. **Leaflet** It should include the proposed text for the leaflet , which should contain at least the following information.
    - Commercial Name
    - Generic Name
    - Pharmaceutical form
    - Strength
    - Content/ volume
    - Number of doses per vial (for multi-doses presentation)
    - Composition
    - Statement of excipients
    - Route
    - Indications
    - Method of use
    - Dosage/ Dose
    - Maximum dose in 24 hours, for OTC products.
    - Precautions
    - Warnings
    - Contraindication
    - Interactions
    - Overdose

- Use during pregnancy and of breast feeding
- Conservation of the product / storage conditions
- Name and address of final product manufacturer
- Name and address of conditioner

22. Monograph for Health Officer: It should submit the drug proposed monograph to be distributed to the health practitioners, if applicable.

23. Final Presentation for Marketing: (according to each country's legislation). Samples or scale models of the main and secondary packaging presentation of the drug should be sent, including leaflet and accessories. This in order to have a representation of the drug that will be marketed, including the accessories, if applicable, and to verify its correspondence with the description in the characteristics of the drug under review.

24. Final product samples: According to the country's legislation, sending of samples shall be required for the corresponding evaluation.

25. Analysis Certificate: Corresponding to the batch of remitted samples.

26. Active Ingredient(s):

- **Chemical Name of the active ingredient**: according to WHO and Pharmacopoeia monograph, as applicable.

- **Manufacturer(s):** (According to the legislation of each country). Indicate name and address of manufacturer(s).

Note: In the case of associations, the information requested here, ***shall be provided individually for each active ingredient that*** is part of the drug.

- **Characteristics:**
  - **Organoleptic:** complete description of the product's organoleptic characteristics, such as color, smell, taste, as applicable.
  - **Physical:** complete description of the physical characteristics of the product.
  - **Chemical:** Complete description of the chemical characteristics of the product.

- **Specifications of the active ingredient.**

- **Analytical method**

- **Validation of the analytical method (when required by the country's legislation)**
- **Shelf life period**
- **In case of New Molecules:**
  - **Structural and molecular formula**
  - **Molecular weight**
  - **Synthesis or obtaining method:** A description of the synthesis or obtaining method should be remitted.
  - **Description of active ingredient:** Including impurities profile and degradation products

27. Final Product:

- **Description and composition of final product:** the description of the final product should be included as well as its composition specifying each one of its components, active ingredient(s) preservation means, stabilizers and excipients, if applicable, stating the function of each one of them.

  In the case of freeze dried products, the description of the diluent should also be included as well as of the container closure system.

- **Pharmaceutical development:** Information on the studies performed to establish the pharmaceutical form, the formulation, the manufacturing process and the container closure system of the drug to be marketed.

- **Manufacturing of the final product:**
  - **Batch formula:** The production batch formula should be supplied including a list of all the components, according to the legislation of each country.
  - **Description of manufacturing process:** It should remit a flowchart of the process identifying the critical steps and the control points of the process, intermediary products and final product.

- **Physical chemical Characteristics of the excipients (**according to the legislation of each country): information on the physical

chemical characteristics and specifications of the excipients used in the formulation of the final product should be supplied.

- **Control of final product:**
  - **Specifications:** the specifications of the final product should be stated.
  - **Analytical Procedures:** Information on the analytical procedures used for quality control of the final product.
  - **Validation of the analytical procedures:** Information on the validation of the analytical procedures of the final product, including experimental data.

- **Standards and reference materials,** according to the legislation of each country, information should be supplied on the standards and/or reference materials used in the control tests of the final product.

- **Description of the container closure system used for the final product:** It should describe in detail the type and form of container and closure system in which the final product is contained, including the materials that constitute said system and quality specifications.

- **Stability of final product,** according to legislation of each country and corresponding climate zone:
  - **Protocols and results of stability study that justify the propose shelf life. :** It should remit a stability study that complies with the current legislation in each country, including study protocol, specifications, analytical methods, detailed description of container and closure system of the product under review, conservation conditions (temperature and room humidity), results of at least three batches of the final product prepared from different batches of active ingredient, conclusions and proposed shelf life for the study. For freeze dried products to prove the compatibility between freeze drying and diluent.
  - **Stability studies program after authorization to market:** It should include the Stability Program or Stability Commitment to be performed in the stage of marketing the final product, including the number of batches to incorporate into the study on an annual basis and the analytical tests to be performed. Each Authority shall establish the mechanisms to confirm the updating of the product's stability information.

- **Shelf life period and conditions of conservation**

- **Description of the procedures used to guarantee the cooling chain:** in the case of products that require refrigeration, to write in detail the measures taken to guarantee the adequate conditions of temperature and humidity to transfer the final product from its production site to the final sale point, including all the storage and distribution stages indicating the controls performed in each one of the stages, this description should be signed by the responsible officer thereof.

29. Biopharmaceutical Documentation: Note: its application is according to WG/BE's recommendation

- Dissolution test (for those pharmaceuticals forms that so require it).
- Studies of bioequivalence in vitro (dissolution profile).
- Studies of bioequivalence in vivo.

30. Non-clinical studies:

- **In case of New Molecules**
  - **Pharmacodynamic Studies**
  - **Pharmacocinetic Studies.**
  - **Toxicology**
    - **General Toxicology:** The following information is required:
      - Design of the study and justification of the animal model
      - Animal species used, age and size of the groups
      - Dose, method of administration and control groups
      - Monitored parameters
      - Local tolerance
    - Special toxicology
      - Special immunologic research.
      - Toxicity studies in special populations.
      - Studies of genotoxicity and carcinogenicity: when applicable.
      - Studies of reproductive toxicity: for drugs to be administered to pregnant women or fertile age individuals.
- **In case of:**
  - **New associations:** recommendations of Technical Report Nº 929, Exhibit 5 of the WHO shall be applied.

- **New substances incorporated into the formulation** (new stabilizers, additives), other methods of administration and new associations, should remit the corresponding toxicology studies.

31. Clinical Studies: Known drugs are excluded (Pharmaceutical Equivalents)

- **Summary of clinical Studies performed.**

- **Phase I Studies:** are mainly directed at defining the pharmacokinetics and bioavailability of the product in the case of **drugs made based on new molecules and new strength.**

- **Phase II Studies: For drugs made based on new molecules, strength , formulation and associations.** These studies are carried out once the Phase I studies have been completed. The main difference between phase I and II is that the Phase II studies involve an important number of subjects and are usually controlled and randomized.

  The phase II studies should define the optimal dose and most important the safety before starting Phase III.

- **Phase III Studies:** These are studies at great scale designed to deliver data on efficiency and safety of the drug. In these studies many thousands of individual can be recruited (this shall be defined by the "end point" of the study).

- **Studies Phase IV – Drug surveillance Plan:** When applicable, according to the type of drug, the protocol of Phase IV studies shall be requested or the results of the studies already carried out.

- **Studies in special populations:** In case of **New Molecules**, according to the drug's indication and each country's legislation.

GLOSSARY

Good Manufacturing Practices (GMP): Set of procedures and practices which ensures drugs batches are consistently produced and controlled to the quality standards for the intended use of said batches according to the conditions demanded for their marketing. Also known as Adequate Manufacturing Practices (AMP) or Good Manufacturing Practices (GMP) or Good Manufacture Practices (GMP).

Product Pharmaceutical or Galenics development: is an essential element knowing all properties and particularities of a product performed to prove that the dose, the formulation, the manufacturing process and the container closure system, as well as microbiological and physicochemical attributes are appropriate for the proposed objective.

Pharmaceutical Equivalents: Drugs that contain the same active ingredient (s), in the same pharmaceutical form, for the same method of administration and that are identical in potency or strength.

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

Batch: A defined quantity of starting material, conditioning material or product, made in a process or series of processes so that it is expected to be homogeneous.
At the end of the final product control, a pharmaceutical product batch comprises all the units of a pharmaceutical form produced from the same materials initial mass and that have suffered a unique series of manufacturing operations or only one sterilization operation or, in case of a continuous production process, all the units manufactured in a determined period of time.
Note: In order to carry out certain preparation phases, it may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch . In continuous manufacture, the batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Known drugs: See Pharmaceutical Equivalents

Distribution Level: Are the limitations established for drug circulation or distribution denominated as: For exclusive use of hospitals, sale under doctor's prescription, free sale or others.

Shelf Life: Is that length of time that medicine is given to maintain the quality specifications established in the drug registration, if conserved correctly according to the manufacturer's recommendations, according to the results of the stability studies performed. It is also known as to be used before, expiry date.

Active Pharmaceutical ingredient (API) Any substance intended to furnish pharmacological activity be used in the manufacture responsible for the therapeutic activity or medicine indication.

Product to be registered: the drug to be registered.

Final bulk product (final bulk): Any product that has completed all the processing stages, not including primary bottling.

Finished Product: A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Drug Registration: Called in some countries License. It is a sanitary procedure via which the National Drug Regulatory Authority grants the corresponding permit to the product in question, for its marketing and distribution in the country, according to the legislation of each country.

Validation: It is a series of documented procedures or actions, in agreement with the Good Manufacturing Practices Principles, that shows that the processes, equipment, materials, activities or systems meet all the predetermined specifications and quality attributes.

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