Pan American Health Organization

Regional Office of the World Health Organization

PANDRH Proposal version 11.04.2008

Pan American Network on Drug Regulatory Harmonization (PANDRH)
Working Group on Vaccines (VWG)

PROPOSED HARMONIZED REQUIREMENTS FOR THE LICENSING OF VACCINES IN THE AMERICAS

INTRODUCTION

Responsibility for the quality, safety and efficacy of vaccines lies first and foremost with the manufacturer. The National regulatory authorities (NRA) in each country must establish procedures to ensure that products and manufacturers meet the established regulatory criteria.

Vaccines are products of biological origin which exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents and adults. Their quality can not be assessed solely by testing the final product alone. It is recommended that the NRAs establish a specific regulatory system for this type of product.

A basic function of NRAs is to evaluate the quality, efficacy and safety of vaccines. This involves authorizing their use, distribution and sale, which implies granting a Market authorization.

In order to license a vaccine, the NRAs must first set requirements for applicants to comply with. These requirements include the information needed in the application file, and evidence that the vaccine has passed the stages of research, development, production and quality control, as well as clinical testing, and that the quality, safety and efficacy required of the vaccine to be used in humans has been established.

Another important aspect to consider in the vaccine evaluation process is that the manufacturing facilities must comply with good manufacturing practices (GMP). The NRA must have a legal authority and regulatory basis so that it can carry out its functions independently, transparently and with authority. Therefore its staff must be trained and have the experience needed to do the evaluation.

BACKGROUND

At the Fourth Conference of the Pan-American Pharmaceutical Regulation Harmonization Network (PANDRH) held in March 2005 in the Dominican Republic, the

establishment of a Vaccines Working Group (Vaccines WG) was proposed in response to a need to develop harmonized documents in this field, and this group was established in June 2005 in Panamá. At its first meeting, the mission, objectives and work plan were determined. As a priority, the Group proposed developing harmonized vaccine registration requirements for the region, using as basic documents the requirements developed for medicines by the Registration Working Group of the PANDRH Network, the document prepared in 1999 by the Pan-American Health Organization (PAHO) on vaccine registration requirements, and the requirements of the countries (Argentina, Brazil, Cuba and Panama) participating in the meeting

Using the information compiled at the first meeting, a survey was designed and sent to all countries in the region in order to find out the requirements applied in each one. This information was processed by the PAHO secretariat in Washington, DC, USA.

At the second meeting of the Vaccines Working Group held in December 2005 in Caracas, Venezuela, all the information sent by 16 countries in the region was reviewed. These countries were Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Uruguay and Venezuela.

Consistent with the PANDRH objectives of harmonizing guidelines and considering all the documentation mentioned previously, as well as other documents such as the Common Technical Document (CTD) of the International Conference on Harmonization (ICH) and the Technical Reports Series of the World Health Organization, the first version of the document on harmonized requirements for the licensing of vaccines in the region was prepared in April 2006 and sent for review by members of the Vaccines WG. It was discussed at the Group's third meeting held in June 2006 in Ottawa, Canada. In July, August and September 2006, the final version of the application guide for the Proposed Harmonized Requirements for the Licensing of Vaccines in the Americas was prepared, expanding on the information already collected.

This document consists of five modules, following the guidelines established by the Common Technical Document (CTD) of the International Conference on Harmonization (ICH), adapted specifically to the market authorization of vaccines.

MODULE I: ADMINISTRATIVE/LEGAL INFORMATION

MODULE II: SUMMARIES

MODULE III: QUALITY INFORMATION
(CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL)

MODULE IV: NON-CLINICAL INFORMATION

MODULE V: CLINICAL INFORMATION

During the evaluation process, the recommendations of the World Health Organization (WHO) for the production and control of the vaccine in question must be considered, as well as good manufacturing practices and clinical and non-clinical evaluation guides published in the WHO's Technical Reports Series.

A guide to applying the Harmonized Requirements for the Licensing of Vaccines in the Americas has been prepared as an attachment to this document in order to provide additional information.

OBJECTIVE

The purpose of this document is to achieve greater harmonization in the information submitted in the application for Market Authorization for human vaccines. Since the same information will be requested and submitted to all countries in the Americas, the licensing process and ultimately the availability of vaccines will be facilitated. It is expected that having a common document will also benefit the region by making more efficient use of technical and financial resources.

SCOPE

Applies to all vaccines to be registered for use in humans, regardless of where they are manufactured, or whether they have been license in another country or not, and considering the current legislation in the country in which registration is sought.

GLOSSARY

The definitions herein apply to the harmonized requirements for the market authorization of vaccines in the Americas and its application guide and are included in this glossary in alphabetical order.

Active ingredient of the vaccine: The antigenic substances (or compounds thereof) that can induce specific responses in humans against an infectious agent, its antigens or toxins.

Batch or lot: Set of final packages of finished vaccine, hermetically sealed, that are homogeneous with respect to the risk of cross-contamination during the packing and freeze-drying processes. Therefore, all final packages must have been filled from a single set of ingredients in a single working session and , if applicable , freeze-dried in standardized conditions in the same room.

Carrier protein: A protein used mainly in conjugated polysaccharide vaccines to which the polysaccharide antigen is linked in order to improve both the magnitude and type of the immune response.

Dosage form: The physical form in which a product is prepared for administration to the recipient.

Shelf life: It is the date before which the quality of the vaccine remains acceptable for its intended use as outlined in the market authorization. It is established based on stability studies.

Final bulk product: Any product that has gone through all stages of processing, including formulation but not final packaging.

Finished product: Final pharmaceutical form that has gone through all steps of the manufacturing process, including final packaging.

Good Manufacturing Practices (GMP): Set of procedures and practices to ensure consistent controlled production of batches of pharmaceutical products, according to proper quality standards for the intended use thereof and the conditions required for their sale.

Lot release: Process for the evaluation of each individual lot of vaccine submitted to be used in the market. This means independent control of each lot to guarantee that all the lots produced and used in a country are in compliance with the established quality specifications. This process can be performed by detailed review of the Summary Protocols of Production and Quality Control including laboratory testing when is feasible.

Market authorization: In some countries it is called a licence. Procedure whereby the national regulatory authority grants permission for the product in question to be sold and distributed in the country.

Master cell bank: Culture of specific cells of known origin that are distributed in a container or packages in a single operation to ensure uniformity and stability in storage. The master bank is usually kept at a temperature of -70°C or less. In some countries, it is called the primary bank.

Product development: All studies to show that the dose, formulation, manufacturing process and packaging system, as well as the microbiological properties, are appropriate for the proposed purpose.

Product to be licensed : Both, the document outlining the harmonized requirements for the market authorization application and its guideline, apply to the registration of vaccines in the in the Americas. The vaccine may be also referred as the product.

Raw materials: Any substance used to make or extract the active ingredient but from which the active ingredient is not directly derived. For example, culture media, fetal bovine serum, etc.

Starting materials: Any substance of biological origin, such as micro-organisms, organs and tissues of plant or animal origin, including cells or fluids of human or animal origin and recombinant cell substrates.

Validation: Series of documented procedures or actions, consistent with good manufacturing practices, demonstrating that the processes, equipment, materials, activities and/or systems satisfy the predetermined specifications and quality attributes.

Working cell bank: Culture of cells derived from a master cell bank and intended to prepare production cultures. The working cell bank is usually kept at a temperature of -70°C or less. In some countries, it is called the secondary bank.

MODULE I: ADMINISTRATIVE INFORMATION

The information in this module depends on the legislation in each country.

1.1 Table of contents (modules 1 to 5)

1.2 Application form

1.2.1 **Proprietary, commercial or trade name of vaccine**

1.2.2 **Non-proprietary name or common name of vaccine**

1.2.3 **Concentration**

1.2.4 **Dosage form**

1.2.5 **Senior Executive Officer / Senior Medical or Scientific Officer:** Name, address, telephone, fax, e-mail

1.2.6 **Legal representative in country**: Name, address, telephone, fax, e-mail

1.2.7 **Market Authorization Holder of the vaccine (for imported products)**: Name, address, telephone, fax, e-mail

1.2.8 **Manufacturer of active ingredient(s)**: Name, address, telephone, fax, e-mail

1.2.9 **Manufacturer of finished product**: Name, address, telephone, fax, e-mail

1.2.10 **Other manufacturers involved in the production process**: Name, address, telephone, fax, e-mail

1.2.11 **Official responsible for releasing batches of finished product**

1.2.12 **Commercial presentation of vaccine**

1.2.13 **Route of administration**

1.2.14 **Conditions of storage or conservation**

1.2.15 **Strength per dosage unit**

1.2.16 **Legal documents on product**: The legal information must be duly certified following the legal procedures of the country of origin and/or the corresponding entity. Legally certified information can be submitted during the evaluation process.

- Document recognizing the technical director or professional responsible for the product
- Authorization of representative
- Certificate of Pharmaceutical Product (CPP)
- Information supporting the implementation of Good Manufacturing Practices of all manufacturers involved in the vaccine production process
- Trademark certificate (optional)
- Patent certificate (under national legislation)
- Batch release certificate issued by NRA (imported products)
- Manufacturer's statement that all relevant information has been included and is accurate

1.3 Summary of product characteristics and product labeling

1.3.1 **Summary of product characteristics**

1.3.2 **Product Labeling**

1.3.2.1 Primary package label

1.3.2.2 Secondary package label

1.3.2.3 Package insert

1.3.2.4 Final packaging

1.3.2.5 Information for health professionals or information for prescription in extended or reduced form

1.3.3 **Samples**

1.3.3.1 Samples of finished product (in accordance with legislation of each country)

1.3.3.2 Summary protocol of batch production and control

1.4 List of countries where the product has been licensed previously

1.5 Information regarding experts

1.6 Environmental risk assessment

MODULE II: SUMMARIES

2.1 General table of contents

2.2 Introduction

2.3 Overall quality summary
- Introduction
- Summary of active ingredient
- Summary of final product

2.4 Overview of non-clinical studies

2.5 Non-clinical summary
- Introduction
- Written summary of pharmacology
- Tabular summary of pharmacology
- Written summary of pharmacokinetics (if applicable)
- Tabular summary of pharmacokinetics (if applicable)
- Written summary of toxicology
- Tabular summary of toxicology

2.6 Overview of clinical studies
- Introduction
- Table of contents
- Detailed discussion of product development

– Overview of immunogenicity
– Overview of efficacy
– Overview of safety
– Conclusions on risk-benefit balance
– Bibliographic references

2.7 Clinical summary

– Introduction
– Table of contents
– Summary of clinical studies of immunogenicity
– Summary of clinical studies of efficacy
– Summary of clinical studies of safety
– Bibliographic references

MODULE III: QUALITY INFORMATION (CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL)

3.1 Table of contents for Module

3.2 Contents

3.2.1 **Active ingredient(s)**: Information must be submitted for each active ingredient in the vaccine.

3.2.1.1 **General information, starting materials and raw materials**

- Trade and/or non-proprietary name(s) of the active ingredient
- Structural formula, molecular formula and relative molecular weight (if applicable)
- Description and characterization of active ingredient
- Analytical certificates signed by the manufacturer and the applicant for registration
- General description of the starting materials
    - Strain
    - System of seed/master/working banks
    - Embryonated eggs
- General description of raw materials

3.2.1.2 **Manufacturing process for the active ingredient**

- Manufacturer(s)
- Description of manufacturing process
- Flow diagram of manufacturing process
- Description of batch identification system
- Identification of critical steps in process and controls
- Description of inactivation or detoxification process
- Description of purification process

- Description of conjugation process
- Stabilization of active ingredient
- Reprocessing
- Filling procedure for the active ingredient, in-process controls
- Selection and justification of critical steps
- Validation of manufacturing process
- Description of changes

3.2.1.3 **Characterization of active ingredient**

3.2.1.4 **Quality control of active ingredient**

- Description of analytical procedures, validation and justification of specifications

3.2.1.5 Reference standards or materials

3.2.1.6 Packaging/container closure system

3.2.1.7 Stability of active ingredient

- Protocol of stability study, results and conclusions

- Post-approval stability program

- Storage and shipping conditions of active ingredient

3.2.1.8 Consistency of production of active ingredient

3.2.2 **Finished product**

3.2.2.1 **Description and composition of finished product**

3.2.2.2 **Pharmaceutical development**

- Active ingredient
- Finished product
- Manufacturing process
- Packaging/container closure system, compatibility
- Justification of final qualitative/quantitative formula

3.2.2.3 **Manufacture of finished product**

3.2.2.3.1 Manufacturer
3.2.2.3.2 Batch formula
3.2.2.3.3 Description of manufacturing process
3.2.2.3.4 Control of critical and intermediate steps
3.2.2.3.5 Validation and/or evaluation process(es)
3.2.2.3.6 Description of batch identification system

3.2.2.4 **Control of adjuvant, preservative, stabilizers and excipients**
3.2.2.4.1 Specifications
3.2.2.4.2 Analytical procedures
3.2.2.4.3 Validation of analytical procedures
3.2.2.4.4 Justification of specifications
3.2.2.4.5 Substances of human or animal origin
3.2.2.4.6 Use of new adjuvants, preservatives, stabilizers and excipients

3.2.2.5 **Control of finished product**
3.2.2.5.1 Specifications
3.2.2.5.2 Analytical procedures
3.2.2.5.3 Analytical certificates signed by manufacturer and applicant for registration
3.2.2.5.4 Validation of analytical procedures
3.2.2.5.5 Consistency and analysis of batches
3.2.2.5.6 Determination and characterization of impurities
3.2.2.5.7 Justification of specifications

3.2.2.6 **Reference standards or materials**

3.2.2.7 **Packaging/container closure system**
- Specifications of primary and secondary packaging
- Tests and evaluation of packaging materials

3.2.3 **Stability**
3.2.3.1 Protocol of stability study, results and conclusions (WHO TRS, 2007)
  - For freeze-dried products, include stability study of freeze-dried material, diluent and reconstituted product
  - Thermostability, where applicable

3.2.3.2 Post-approval stability program
3.2.3.3 Description of procedures to guarantee cold chain

3.2.A **Appendix** : Some authorities require that the following information be included in the appendices of Module III.

3.2.A.1 **Equipment and facilities**

3.2.A.2 **Safety evaluation of adventitious agents**

3.3 Bibliographic references

MODULE IV: NON-CLINICAL REPORTS

The non-clinical studies should follow the guidelines of the World Health Organization (WHO) Guide on non-clinical evaluation of vaccines, Technical Report Series No. 927, WHO, 2005, or the current edition thereof.

4.1 Table of contents of the Module

4.2 Reports on studies

4.2.1 **Pharmacology**

4.2.1.1 Pharmacodynamic studies (immunogenicity of vaccine)

4.2.1.2 Pharmacodynamic studies of adjuvants (if applicable)

4.2.2 **Pharmacokinetics**

4.2.2.1 Pharmacokinetic studies (in case of new adjuvants, new modes of administration)

4.2.3 **Toxicology**

4.2.3.1 **General toxicology** — information on:

- Design of study and justification of animal model
- Animal species used, age and size of groups
- Dose, mode of administration and control groups
- Monitored parameters
- Local tolerance

4.2.3.2 **Special toxicology** (for vaccines to which it applies)

- Special immunological investigations
- Toxicity studies on special populations
- Studies of genotoxicity and carcinogenicity

4.2.3.3 **Toxicity of new substances used in formulation** (new adjuvants, stabilizers, additives)

4.2.4 **Special considerations**

4.2.4.1 **For attenuated vaccines**, evaluation of possible “shedding” (excretion) of micro-organism

4.2.4.2 **Toxicity of new substances used in formulation** (new adjuvants, stabilizers, additives), other modes of administration or new combined vaccines — the appropriate toxicological studies must be provided

4.3 Bibliographic references

MODULE V: REPORTS OF CLINICAL STUDIES

The information should be consistent with the WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations (WHO Technical Report Series, 924, 2005, or latest edition) and regulatory guidelines in each country.

5.1 Table of contents of the Module

5.2 Contents: Reports of clinical studies

5.2.1 **Phase I studies**

5.2.2 **Phase II studies**

5.2.3 **Phase III studies**

5.2.4 **Special considerations**

5.2.5 **Adjuvants**

5.2.6 **Phase IV studies and / or Pharmacovigilance Plan** (if applicable)

5.2.7 **Non-inferiority studies** (for combined vaccines, or approved vaccines prepared by new manufacturers)

5.2.8 **Co-administration studies with other vaccines**

5.3 Bibliographic references

ABBREVIATIONS

CID: Common International Denomination

COTCS: Certificate for over-the-counter sale

CTD: Common Technical Document of ICH

GMP: Good Manufacturing Practices

ICH: International Conference on Harmonization

NRA: National Regulatory Authority, also known as National Regulatory Agency and Drug Regulatory Authority

PAHO: Pan American Health Organization

CPP: Certificate of Pharmaceutical Product

Vaccines WG: Vaccines Working Group

WHO: World Health Organization

PANDRH: Pan American Network on Drug Regulatory Harmonization • Guidance for Industry. ICH M4: Organization of CTD. August, 2001. Center of Biological Evaluation and Research (FDA)

BIBLIOGRAPHY

• Guidance for Industry. ICH M4Q: The CTD -Quality. August 2001. Center of Drugs Evaluation and Research (FDA)
• Guidance for Industry. ICH M4S: The CTD- Safety. August, 2001. Center of Biological Evaluation and Research, Center of Drugs Evaluation and Research (FDA)
• Guidance for Industry. ICH M4E: The CTD- Efficacy. August, 2001. Center of Biological Evaluation and Research, Center of Drugs Evaluation and Research (FDA)
• Guidelines for national authorities on quality assurance for biological products. In WHO Expert Committee on Biological Standardization. Forty-second Report. Geneva. WHO, 1992. TRS No. 822: 31-46.
• Guidelines on clinical evaluation of vaccines: regulatory expectations. WHO Technical Report Series 924, 2005.
• Guidelines on non-clinical evaluation of vaccines. WHO Technical Report Series 927, 2005.
• Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva. WHO, 2003 (WHO/BCT/QSD/03.01)
• Griffiths E, Knezevic I. Assuring the quality and safety of vaccines: regulatory expectations for licensing and batch release. In: Robinson A, Cranage M, Hudson M, eds. Methods in molecular medicine: vaccine protocols. Totowa New Jersey. Humana Press, 2003, 353-376.
• Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 2 Updated edition: Good manufacturing practices and inspection. World Health Organization. Geneva, 2004.
• Requirements harmonized for the Sanitary Registration of Vaccines in the Region. PAHO, 1999 (unpublished document)
• Tabulation of the survey: Requirements for the Sanitary Registration of vaccines. Working group of Vaccines of the Network PANDRH. Prepared in September, 2005. (unpublished document)

Note: The present document doesn't follow the same numbering sequence than the CTD (ICH document), however responding to the request from several institutions during the public opinion, the numbering will be change to follow the CTD numbering sequence