PANDRH Guidelines version 11/04/2008

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

PROPOSED HARMONIZED REQUIREMENTS FOR THE LICENSING OF VACCINES IN THE AMERICAS

GUIDELINES FOR PREPARATION OF APPLICATIONS

Introduction

This document is intended to provide additional guidance to industry for the preparation of submissions according to the document Harmonized Requirements for Licensing Vaccines in the Americas.

The information required is structured using the International Conference on Harmonisation (ICH) Common Technical Document (CTD) format and complemented with the Recommendations for vaccines published in the World Health Organization's Technical Report Series.

Each country has its own application form for market authorization based on its own legislation. The minimum information to be presented by the applicant has been harmonized by the Working Group on Vaccines of the Pan American Network for Drug Regulatory Harmonization (PANDRH) for licensing vaccines in the Americas. Because of their special characteristics, vaccines should always be considered as new products for the purposes of market authorization.

In some countries, information on the manufacturer is considered to be part of the registration file and in others not, depending on the organizational structure of the national regulatory authority.

MODULE 1. ADMINISTRATIVE INFORMATION

The information requested in this module depends on each country's legislation. The requirements include:

1.1 **Index**. The application to license vaccines should include an index of the information contained in each module.

1.2 **Market authorization application form**. Each country has a specific form based on its legislation, the minimum information to be provided in that form is:

1.2.1 **Proprietary ,commercial or trade name of the vaccine**. The name under which the vaccine will be marketed.

1.2.2 **Non-proprietary or common name of the vaccine**. The name adopted by the World Health Organization, the common international name, or the name contained in official pharmacopeias recognized in the country.

1.2.3 **Concentration**. State the concentration of the active ingredient(s) contained in the vaccine.

1.2.4 **Dosage form**. Indicate the dosage form of the vaccine, for example, injectable solution, lyophilized power for injectable suspension.

1.2.5 **Senior Executive Officer / Senior Medical or Scientific Officer**. The professional responsible for the product in the country where market authorization is applied for. Name, address, telephone number, fax, e-mail, professional licence number, and the registration number of his/her degree, as per the country's legislation.

1.2.6 **Legal representative in the country**. Refers to the company that represents the product, which will be responsible for marketing it in the country. Give the full name, address, telephone, fax, and e-mail. Some countries in the region do not require legal representatives resident in the country to obtain market authorization of a product.

1.2.7 **Market authorization holder of the vaccine (for imported products)**. Give the full name of the market authorization holder of the vaccine if licensed in the country of origin, also information of the institution: address, telephone, fax, and e-mail.

1.2.8 **Manufacturer of the active ingredient(s)**. Give the name, address, telephone, fax, and e-mail of the manufacturer(s) involved in the production of the active ingredient(s) in the vaccine.

1.2.9 **Manufacturer of the finished product**. Give the name, address, telephone, fax, and e-mail of the manufacturer(s) involved in the production of the finished product.

1.2.10 **Other manufacturer(s) involved in the production of the vaccine**. In the event that some parts of the manufacturing process are performed by a different company, give name, address, telephone, fax, and e-mail. For

lyophilized vaccines, include the name, address, telephone, fax, and e-mail of the producer of the diluent.

1.2.11 **Person responsible for release of the lots of finished product**. Give the name and position of the person responsible for the release of the lots of vaccine.

1.2.12 **Commercial presentation of the vaccine**. Indicate whether the vaccine is offered for sale in single or multiple doses presentation and whether it will be distributed in a single package or in a multi unit package and whether it contains any additional accessories, for example a transfer device.

1.2.13 **Route of administration**. Indicate the route of administration of the vaccine.

1.2.14 **Storage conditions**. Indicate the storage temperature for the vaccine and any other storage conditions, for example: protect from light, do not freeze.

1.2.15 **Strength of each unit of dose**

1.2.16 **Legal documents on the product**. The legal information should be duly certified, authenticated under the procedure in effect in the country of origin, and issued by the appropriate entity. The certified documents may be presented during the license process and they won't constitute a limitation for the dossier submission.

Document confirming the Senior Executive Officer / Senior Medical or Scientific Officer responsible for the product (under the country's legislation). Submit a document issued by the manufacturer of the vaccine giving information regarding the individuals responsible for the product in the country indicating who is authorized to perform the related regulatory activities, including application for market authorization of the vaccine.

- **Authorization of the representative or representative's letter**. Document issued by the manufacturer of the vaccine authorizing the company to represent it and market the vaccine in the country.

- **Certificate of Pharmaceutical Product (CPP),** using the WHO model. Required for imported vaccines since it is the certificate issued by the regulatory authority that grants market authorization in the country of origin. This certificate includes information on compliance with good manufacturing practices (GMP). Some countries issue a free sale certificate, this should be submitted in addition to the GMP certificate.

- **Information supporting the implementation of good manufacturing practices of other manufacturers involved in the production of the vaccine:** this should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the active

ingredient(s), the diluent, and those responsible for labelling and packaging the finished product. It is important that the certificate indicates the procedures that the establishment is authorized to perform.

- **Trademark certificate** (optional)

- **Invention patent certificate** (based on the country's legislation)

- **Lot release certificate**. Refers to the lot release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for licensing , as applicable.

- **Manufacturer's declaration,** A document should be presented certifying that the information provided is the information corresponding to all the studies performed, regardless of their results. These include all the pertinent information regarding all toxicological and/or clinical tests or trials of the vaccine that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

1.3 **Summary of product characteristics and product labelling**

1.3.1 **Summary of the characteristics of the product**. A summary should be submitted of the characteristics of the vaccine under evaluation.

1.3.2 **Product Labelling** The text proposed for the primary label, the secondary label or exterior packaging, and the package insert should be included.

1.3.2.1 **Primary package label:** Submit the label proposed for the vaccine's primary package or container, which should provide the following information as a minimum:

Proprietary , commercial or trade name
Non-proprietary name or common name
Dosage form
Concentration, potency, or viral titre
Content/volume
Volume/dose
Number of doses per vial (for multidose presentations)
Route of administration
Storage temperature (if the size of the package so permits)
Warnings
Lot number
Expiry date
Manufacturer

Registration number

1.3.2.2 **Secondary Package Label**. Include the text proposed for the vaccine's secondary packaging, also known as the packaging that protects the primary vaccine container, which should provide the following information as a minimum:

Proprietary , commercial or trade name
Non-proprietary name or common name
Dosage form
Concentration, potency, or viral titre
Content/Volume
Volume/dose
Number of doses per vial (for multidose presentations)
Composition
Excipients
Product storage
Route of administration
Instructions for preparation
Mode of use
Warnings
Distribution level
Identification marks (some countries require that an identification mark indicating the type of product be included, for example a yellow band for paediatric products).
Lot number
Date of expiry
Name and address of the manufacturer of the finished product
Name and address of the company responsible for packaging
Name and address of the owner, representative, or distributor
Name of the professional in charge
Registration number

1.3.2.3 **Package insert.** Include the text proposed for the package insert, which should contain the following information as a minimum:

Proprietary, commercial or trade name
Non-proprietary or common name
Pharmaceutical form
Concentration, potency, or viral titre
Content/Volume
Volume/dose
Number of doses per vial (for multidose presentations)
Composition
Excipients
Cell substrate
Route of administration

Indications
Immunization plan
Proper use
Precautions
Warnings
Adverse events allegedly associated with vaccination and immunization
Contraindications
Use during pregnancy and breast feeding
Storage of the product/storage conditions
Name and address of the manufacturer of the finished product
Name and address of the company responsible for packaging

1.3.2.4 **Final packaging**. Samples, or alternatively labels and cartons, of the primary and secondary packaging of the vaccine, including the package insert and accessories should be submitted. The purpose of this is to–provide an example of the vaccine, including accessories, if any, to verify that they correspond to what is described for the characteristics of the vaccine under evaluation.

1.3.2.5 **Information for health professionals**. Submit the proposed information on the vaccine to be distributed to health professionals.

1.3.3 **Samples**

1.3.3.1 **Samples of the finished product**. In accordance with the country's legislation, samples must be sent for the corresponding analytical evaluation.

1.3.3.2 **Summary protocol of batch production and control:** This protocol should follow the format recommended by the WHO in the specific requirements for the production and control of the specific vaccine submitted for market authorization. These protocols are published in the WHO's Technical Report Series. For novel vaccines for which there are no specific WHO recommendations, submit a template of the protocol proposed for its evaluation or a protocol that has been approved by the regulatory authority of the country of origin.

1.4 **List of countries where the product has already been licensed and summary of the approval conditions**. The list of countries where the vaccine is registered at the time the application for registration is submitted or, if there are none, the countries where registration is being processed. In the event the product has been registered in other countries, attach the summary of the conditions under which the market authorization was granted by that regulatory authority.

1.5 **Information regarding experts**. A declaration should be sent signed by each of the experts who performed the product evaluation from the standpoint of

quality, nonclinical studies and clinical studies. Attach a summary of their academic records and employment experience and state the professional relationship between the experts and the applicant of market authorization.

1.6 **Environmental risk assessment:** Include an evaluation of the possible environmental risks posed by the use and/or disposal of the vaccine and give proposals in that regard and the indications or warnings to be included on the product label.

MODULE II: SUMMARIES

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological), nonclinical and clinical information presented in modules III, IV, and V in the market authorization application. The experts who draft these summaries should take an objective approach to the decisive points related to the quality of the vaccine, clinical and nonclinical studies performed, report all pertinent data for the evaluation, and refer to the corresponding tables included in modules III, IV, and V. The information in module II should be presented in the following order:

2.1 **General table of contents**. A general index should be included of the scientific information contained in modules II to V.

2.2 **Introduction**. A summary of the type of vaccine, composition, immunological mechanism, and indications proposed for the vaccine.

2.3 **Overall quality summary**. A general summary of the quality of the vaccine should be presented, related to the chemical, pharmaceutical, and biological aspects. This summary should refer exclusively to the information, data, and justifications included in module III or in other modules of the registration document. The format to be followed is:

- Introduction
- Summary of the active ingredient
- Summary of the finished product

2.4. **Overview of the nonclinical studies:** A comprehensive and critical assessment of the results of the evaluation of the vaccine in animals and in vitro testing should be presented and the safety characteristics of the vaccine for use in humans should be defined. The data should be presented as a written and tabulated summary, in the following order:

- Introduction
- Written pharmacological summary
- Tabulated pharmacological summary
- Written pharmacokinetic summary (when appropriate)
- Tabulated pharmacokinetic summary (when appropriate)
- Written toxicological summary

- Tabulated toxicological summary

2.5. **Nonclinical summary**. A summary of the results of the pharmacological, pharmacokinetic, and toxicological tests on animals and/or in vitro. An objective written and tabulated summary should be presented in the following order.

- Introduction
- Written pharmacological summary
- Tabulated pharmacological summary
- Written pharmacokinetic summary (when appropriate)
- Tabulated pharmacokinetic summary (when appropriate)
- Written toxicological summary
- Tabulated toxicological summary

2.6 **Overview of the clinical studies:** Should present a critical analysis of the clinical results included in the clinical summary and in module V. Should include a summary of the clinical development of the vaccine, the design of the pivotal studies, and the decisions related to the clinical studies and their performance. Should include an overview of the clinical conclusions and an evaluation of the risks/benefit in relation to the results of the clinical studies and justification of the proposes dosages. All the data related to efficacy and safety assessed through the development of the vaccine will be presented, as well as any outstanding problems. The data should be presented in a written and tabulated summary in the following order:

- Introduction
- Index
- Detailed discussion of the development of the product
- Overview of immunogenicity
- Overview of the efficacy
- Overview of the safety
- Conclusions and risk/benefit analysis
- Bibliography

2.7 **Clinical summary**. A critical summary of the results submitted in module V. This summary should include of all the clinical studies performed. It should also present a synopsis of each study. The summary of clinical information should be in the following order:

- Introduction
- Index
- Summary of the clinical immunogenicity studies
- Summary of the clinical efficacy studies
- Summary of the clinical safety studies
- Bibliography

MODULE III. INFORMATION ON QUALITY (CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL)

3.1 **Module index**. In accordance with the general plan described in the document on Harmonized Requirements for the Licensing of Vaccines in the Americas.

3.2 **Content**. Corresponds to the basic principles and requirements of the active ingredient(s) and finished product. Includes the chemical, pharmaceutical, and biological data on development, the manufacturing process, certificates of analysis, characterization and properties, quality control, specifications and stability of each of the active ingredients and finished product, as indicated below.

3.2.1 **Active ingredient(s)**. The information requested under this point should be supplied individually for each antigen in the vaccine.

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

- Name of the active ingredient based on the WHO or pharmacopoeial requirements, as appropriate.

- Structural and molecular formula and relative molecular mass, when applicable, for example in synthetic vaccines containing polysaccharides or proteins. In this case, include the schematic amino acid sequence, indicating the glycosylation sites or other modifications and relative molecular mass.

- Description and characterization of the active ingredient, including physicochemical properties and biological activity.

- General description of the starting materials of biological origin used to obtain or extract the active ingredient. For each biological starting material include a summary of viral safety of the material:

    - Strain. Information on the origin, number of passes, identification, analysis certificates, processes of attenuation, development or construction and genetic stability, depending on the type of vaccine strain.

    - Master/working seed bank systems - origin, identification, characterization, preparation method, analysis certificates, determination of foreign agents, stability, controls, and frequency of the tests, definition of the number of passes. In the case of cell banks, demonstrate that the characteristics of the cells remain unaltered in the passes used in production and successively.

  - Use of fertilized eggs. Information on their origin, identification, quality certificates.

- General description of the raw materials. Considering the raw materials used in the preparation process from which the active ingredient is not directly derived, such as culture media, bovine fetal serum, etc. Submit information on manufacturer(s), quality certificates, controls performed. In the case of raw materials of animal origin, describe the origin and criteria for selection, shipping, and conservation, and submit a certificate on reduction of the risk of transmission of agents related to animal spongiform encephalopathy.

3.2.1..2 **Manufacturing process for the active ingredient**

- Manufacturer(s). Give the name, address, and responsibilities of the manufacturer(s).

- Description of the manufacturing process of the active ingredient. Submit a description of the manufacturing process that includes all the stages. A typical production process for a vaccine starts with a vial(s) from the respective seed and / or cell bank, including cell cultures, harvest(s), purification, modification reactions (when applicable), filling, storage, and transfer conditions. Where applicable, include the number of passes.

- Flow chart of the production process, showing all the manufacturing steps, including intermediate processes.

- Description of the lot identification system. Identification of the lot in each stage of the process, including when mixtures are made. Also submit information on the manufacturing scale and lot size.

- Identification of critical steps in the process and controls performed, from the original inoculation until the active ingredient is obtained, defining the operational parameters or aspects to be controlled during the critical stages, including acceptance criteria.

- Description of the inactivation or detoxification process when applicable. Methods and agents used, parameters controlled, and production stage in which it is performed.

- Description of the purification process. Method used, reagents, and materials used, operating parameters controlled, and specifications. Conditions for the use and re-use of membranes and chromatography columns and the respective validation studies.

- Description of the process for conjugation and/or modification of the active ingredient, when applicable. Also include information on the origin and

quality control of the starting material used to obtain the substance used as protein carrier.

- Stabilization of the active ingredient. Description of the steps performed to stabilize the active ingredient, for example, the addition of stabilizers or other procedures, when applicable.

- Reprocessing. Description of the procedures established for reprocessing the active ingredient or any intermediate product; criteria and justification.

- Procedure for filling the active ingredient, process controls, storage and transport. Description of the procedure for packaging the active ingredient, process controls, acceptance criteria, type of container closure system, type of seal on the container used to store the active ingredient, storage and transfer conditions, when applicable.

- Selection and justification of critical stages in the manufacturing process, process controls, and acceptance criteria.

- Validation of the manufacturing process. Information on validation procedures and/or evaluation of the manufacturing procedures, including reprocessing, establishment of critical steps, and criteria for establishing the control limits on the critical steps.

- Description of changes. Describe and justify significant changes in the production process of the active ingredient during development. State the number of lots prepared during development, production scale, use of each lot, for example stability study, nonclinical or clinical study.

3.2.1.3 **Characterization of the active ingredient**. Present data to determine the structure and physicochemical, immunological, and biological characteristics of the active ingredient.

3.2.1.4 **Quality control of the active ingredient**

- Description of the analytic procedures, validation, and justification of the quality specifications.

- Production consistency. Summarized protocol of the production and control of three consecutive lots of active ingredient, analysis certificates in the event this information is not included in the summarized protocol for the finished product, an analysis of the results of these lots in terms of production consistency.

3.2.1.5 **Reference standards or materials**. Detailed description of the reference standards or materials used and analysis certificates.

3.2.1.6 **Packaging and container closure system of the active ingredient**. Full description of the packaging and container closure system in which the active ingredient will be stored until used for preparing the finished product. The information should include identification of all the materials that constitute the packaging container closure system and their specifications. When applicable, discuss the types of materials selected with respect to protection of the active ingredient against humidity and light.

3.2.1.7 **Stability of the active ingredient**

- Protocol for the stability study, results and conclusions. Should include the study conditions, including all the storage conditions (temperature, humidity, light) in which the vaccine is evaluated, analytical method, specifications, results, and conclusions.

- Stability program or stability commitment. Refers to the continuation of the stability study, including the number of lots to be included in the study each year and the tests to be performed.

- Storage and transportation conditions for the active ingredient, when applicable. Describe the equipment used, areas, and buildings (if pertinent) and the shipping and storage conditions.

3.2.2 **Finished product**

3.2.2.1 **Description and composition of the finished product**. This should include a description of the finished product, its composition, listing each of the components, active ingredient(s), adjuvants, preservatives, stabilizers, and excipients, stating the function of each of them.

For lyophilized products, also include a description of the diluent and the container closure system employed for the diluent.

3.2.2.2 **Pharmaceutical development** Information on the studies performed to established the dosage form, formulation, manufacturing process, and the container closure system used for final product. The studies described in this point are different from the routine quality control tests performed in accordance with the product specifications. Include the following aspects:

- Active ingredient. Compatibility with the rest of the components in the finished product, including adjuvant, preservative, stabilizers, as applicable.

- Finished product. Development of the formulation, considering the proposed route of administration. Physicochemical and biological properties of the product, indicating the relevant parameters for developing the finished product.

- Development of the manufacturing process. Description of the selection and optimization of the manufacturing process, particularly for critical aspects.

- Container closure system selected. Information on the materials selected, protection against humidity and light, compatibility of the materials.

3.2.2.3 **Manufacture of the finished product**

- Manufacturer. Name, address, and responsibilities of each manufacturer involved, including contract manufacturers for production and quality control.

- Lot formula. Provide the formula of the production lot, including a list of all components.

- Description of the manufacturing process. Submit a flowchart of the process, including all the steps in the process and indicate the points at which the material enters the process, identify the critical steps and control points in the process, intermediate products, and final product. Also include a narrative of the manufacturing process, the in process controls, and the critical points identified.

- Control of critical and intermediate steps. Tests and acceptance criteria developed to identify the critical steps in the manufacturing process and how they were controlled.

- Validation and/or evaluation of the processes. Description, documentation, and results of the studies on validation and/or evaluation of the manufacturing process, including the critical steps or critical tests employed in the manufacturing process. It is also necessary to provide information on the viral safety of the product, when applicable.

3.2.2.4 **Control of the adjuvant, preservative, stabilizers, and excipients.**

- Specifications. Provide information on the specifications for all the substances employed in the formulation of the finished product that are different from the active ingredient.

- Analytical procedures. Description or bibliographic reference of the methods used to control these substances.

- Validation of the analytical procedures used to control the substances used in formulating the final product.

- Justification of specifications of the substances used in formulating the final product.

- Human or animal substances. Provide information on the source, origin, description of the quality tests performed, specifications, determination of adventitious agents, and viral safety.

- New adjuvant, preservative, stabilizer, and excipients. When used for the first time in a vaccine for human use or for a new route of administration, provide all information on the manufacture, characterization, and control, and data supporting safety established in nonclinical and clinical studies in relation to the active ingredient used.

3.2.2.5 **Control of the finished product**

- Specifications. Indicate the specifications for the finished product.

- Analytical procedures (summaries or references not accepted). Information on the analytical procedures used for quality control of the finished product.

- Validation of the analytical procedures. Information on the validation of the analytical procedures for the finished product, including experimental data.

- Lot consistency and analysis. The production and control protocols for at least three lots of finished product should be submitted and an analysis of the results for those lots in terms of production consistency.

- Characterization and/or determination of impurities, as applicable, depending on the method used to manufacture the vaccine submitted for market authorization.

- Justification of specifications. Provide justification of the specifications proposed for the finished product.

3.2.2.6 **Reference standards and materials.** Provide information on the reference standards and/or materials used in the tests to control the finished product.

3.2.2.7 **Description of the container closure system used for the finished product**. Describe in detail the type and form of container closure system of the finished product, including the materials of which they are made and quality specifications.

3.2.3 **Stability of the finished product**

- Protocols and results of the stability study that justify the proposed validity period. Submit the stability study that complies with each country's legislation, including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product

evaluated, storage conditions (temperature and relative humidity), results for at least three lots of finished product prepared from different lots of active ingredient, conclusions, and proposed validity period. The stability studies should be signed by the professional in charge of the study. It is important to provide additional studies on the stability of the vaccine in intermediate stages in the manufacturing method that require different temperatures from the storage temperature, studies of challenge temperatures, photosensitivity or other specifications, depending on the type of vaccine, evaluated for at least three lots. For lyophilized vaccines demonstrate the compatibility between the lyophilized product and the diluent.

- Post-approval stability program. Include the stability program or stability commitment to be carried out once the vaccine is in the market, including the number of lots to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the vaccine evaluated.

- Description of the procedures used to guarantee the cold chain. Describe in detail the measures used to guarantee adequate temperature and humidity conditions for shipping the finished product from the place of production to the place of final sale, including all the storage and distribution stages and indicating the controls performed in each of the stages. This description should be signed by the professional responsible for it.

3.2.A **Appendix** Some authorities require the following information in the appendixes to Module III.

3.2.A.1 **Equipment and facilities**. Diagram illustrating the production flow, including materials, personnel, waste, and intermediate products in relation to the manufacturing areas; information on adjacent areas related to protection and maintenance of the integrity of the vaccine.

Also submit information on all the products prepared and/or handled in the same areas as the product submitted for market authorization. Describe the procedures to avoid cross-contamination of areas and equipment.

3.2.A.2 **Evaluation of the safety of adventitious agents**: Additional, detailed information on evaluation of the safety of the product in relation to adventitious agents of both viral and non-viral origin.

MODULE IV . NON-CLINICAL REPORTS

Non-clinical studies should comply with the World Health Organization's Guidelines on Non-clinical Evaluation of Vaccines, WHO Technical Series No. 927, 2005, or most recent version.

4.1 Module index

4.2 Reports on studies

4.2.1 Pharmacology

4.2.1.1 Pharmacodynamic studies (immunogenicity of the vaccine)

4.2.1.2. Pharmacodynamic studies of adjuvants (if applicable)

4.2.2 Pharmacokinetics

4.2.2.1 Pharmacokinetic studies, when applicable depending on the type of vaccine or when new substances are used in the formulation of the product, new routes of administration, or pharmaceutical forms that require the respective pharmacokinetic evaluation.

4.2.3 Toxicology

4.2.3.1 **General toxicology**. Information should be presented on:

- Design of the study and justification of the animal model
- Animal species used, age, group size
- Dose, route of administration, and control groups
- Parameters monitored
- Local tolerance

4.3.3.2 **Special toxicology for vaccines** (when applicable)

- Special immunological investigations
- Toxicity studies in special populations
- Genotoxicity and carcinogenicity studies, when applicable
- Reproductive toxicity studies for vaccines to be administered to pregnant women or individuals of fertile age.

4.2.4 Special considerations

4.2.4.1 **Live attenuated vaccines**. An evaluation should be presented of the possibility of microorganism shedding through natural avenues of excretion.

4.2.4.2 **In the case of new substances incorporated into the formulation** (new adjutants, stabilizers, additives) other routes of administration, and new combined vaccines, submit the corresponding toxicology studies.

MODULE V. REPORTS ON CLINICAL STUDIES

The clinical studies should follow the World Health Organization's Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations. WHO Technical Series No. 924, 2005, or most the recent version, and each country's regulatory guidelines.

General comments

Before beginning the clinical studies, it is necessary to have in-depth knowledge of the epidemiology of the pathogens or disease of interest in the study population. This knowledge makes it possible to statistically define the size of the sample required for the studies and to weigh the magnitude of the results for efficacy and safety.

All clinical studies should comply with the international standards for good clinical practices.

The clinical studies necessary to evaluate the clinical efficacy of a vaccine that contains one or more new antigens can involve substantial requirements with regard to the size of the population, compared to known and previously-evaluated antigens. It is reasonable to require immunogenicity and safety studies only for vaccines that contain known, widely-used antigens and where correlates of protection have been well established.

5.1 Index of the module

5.2 Reports of Clinical studies

5.2.1 **Phase I studies**. These are intended to define the safety and reactogenicity of the vaccine and to seek preliminary information on immunogenicity. Dose and route of administration should be evaluated with respect to these parameters. Generally these studies are conducted on small groups of immunocompetent healthy adults (50 to 200) who present low risk of being infected by the vaccine or related complications.

5.2.2 **Phase II studies**. After the studies in phase I have been completed or sufficient information is obtained to demonstrate satisfactory results, the phase II studies can begin. The main distinction between the two phases, is that the phase II studies involve a large number (200 to 600) of subjects and are usually controlled and randomized. The main objectives of these studies are to demonstrate the immunogenicity of the active component(s) and safety in the target population (mainly healthy children). The phase II studies should define the optimum dose, the vaccination schedule, and most importantly, safety, prior to beginning phase III.

5.2.3 **Phase III studies**. The Phase III studies are large scale studies designed to obtain data on the efficacy and safety of the vaccine. These studies are

usually carried out in large populations to evaluate the efficacy and safety to the formulation(s) of the immunologically active component(s). Several thousand subjects can be enrolled in these studies (the number will be defined by the end point of the study). Serological data are collected (for at least one immunized population subgroup) with the idea of establishing a correlation between clinical efficacy and immunogenicity, although this cannot always be established.

The type of vaccine and other relevant factors (incidence of disease, immunological markers, and safety) will determine the duration of the follow-up on these studies and the number of participants.

The phase III clinical studies should be performed using at least three lots manufactured on the industrial or production scale to be used routinely (in the majority of countries).

5.2.4 **Special considerations**. Depending on the type of vaccine, apart from the clinical studies on immunogenicity, efficacy, and reactogenicity, it may be necessary to evaluate microorganism shedding in the case of live vaccines, interaction with other vaccines, and interference with maternal antibodies.

5.2.5 **Adjuvants**. Evidence and scientific support that justifies the use of adjuvants, when applicable.

5.2.6 **Phase IV studies**. Depending on the type of application for market authorization, approval in other countries, or depending on the type of vaccine, a phase IV study protocol or the results of studies that have already been performed, will be required.

For new vaccines, a pharmacovigilance plan should be presented.

5.2.7 **Combined vaccines or vaccines made by new manufacturers.** Submit information on bridging studies performed to ensure the non-inferiority of the vaccine under evaluation compared with the reference vaccine, supporting immunogenicity, reactogenicity, safety, and efficacy, when applicable.

5.3 Bibliography

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