Health Canada Santé Canada

Draft Guidance Document

Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application

This guidance document is being distributed for comment purposes only.

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Table of Contents

1. 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 that exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents and adults. The quality of a vaccine cannot be assessed solely by testing the final product alone. It is recommended that NRAs establish a specific regulatory system for vaccines.

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

In order to license a vaccine for human use, the NRA must first set requirements for applicants to comply with. These requirements include the following:

- information needed for the application;
- evidence that the vaccine has passed the stages of research, development, production and quality control;
- evidence from clinical testing, and
- evidence that the vaccine's quality, safety and efficacy 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 legal authority and regulatory basis so that it can carry out its functions independently, transparently, and with authority. NRA staff must be trained and have the experience needed to do the evaluation.

1.1 Background

At the Fourth Conference of the Pan American Network for Drug Regulatory Harmonization (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.

The Vaccines WG was established in June 2005 in Panama where it determined its mission, objectives and work plan. As a priority, the Vaccines WG proposed developing

harmonized vaccine registration requirements for the Pan American Region (Region) by using the following as a base:

- the requirements developed for medicines by the PANDRH Working Group on Medicines Registration;
- the document prepared in 1999 by the Pan American Health Organization (PAHO) on vaccine licensing requirements; and,
- the requirements of the countries participating in the meeting (Argentina, Brazil, Cuba, and Panama).

Using the information compiled at the first meeting, a diagnostic survey was designed and sent to all countries in the Region to find out which requirements applied in each one. This information was processed by the PAHO Secretariat in Washington D.C., USA.

In December 2005, in Caracas, Venezuela, the Vaccines WG reviewed all of the information sent by 16 countries in the Region in response to the diagnostic survey. These countries were Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Uruguay, and Venezuela.

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 the Vaccines WG members. The document is consistent with the PANDRH objectives of harmonizing guidelines and considers the base requirements mentioned above, as well as the International Conference on Harmonization (ICH) Common Technical Document (CTD) and the Technical Report Series of the World Health Organization (WHO).

In June 2006, the document was discussed at the Vaccines WG's third meeting 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.

The document was then distributed for public consultation. In October 2008, a meeting was held in Washington D.C. with NRAs and industry to analyze the comments received. The most common comment received was that the same numbering and structure of the ICH should be used. An updated version was presented for approval at the V Conference of PANDRH, held in Argentina, in November 2008.

In September 2012, the Vaccines WG members (from Argentina, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador,

Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Trinidad & Tobago and Venezuela) met in Ottawa, Canada to discuss implementation of the harmonized requirements for the licensing of vaccines. The main challenge to implementing the document for some countries was related to the deviation from the ICH CTD format with respect to the module section titles and numbering. Based on the meeting recommendations, the document was modified to align with the ICH CTD format. This version is a result of the modification.

This document consists of five modules, following the guidelines established by the ICH CTD, adapted specifically to the licensing of vaccines.

Module 1. Administrative Information and Prescribing Information
Module 2. Common Technical Document Summaries
Module 3. Quality
Module 4. Nonclinical Study Reports
Module 5. Clinical Study Reports

1.2 Objectives

The objective of this document is to establish harmonized requirements for the submission of licensing applications for vaccines for human use. Requiring the same level of information across countries will facilitate the licensing process and ultimately the availability of vaccines. It is expected that having a common document will also benefit the Region by making more efficient use of technical and financial resources.

1.3 Scope and Application

This document applies to all vaccines to be authorized for human use, regardless of where they are manufactured, whether they are licensed in the country of origin or not, and considering the current legislation in the country in which a licence for a vaccine is sought.

Health Canada's Biologics and Genetic Therapies Directorate is adopting this document for use in Canada. Guidance specific to Canadian submissions is presented in bold and italics font.

***In Canada, sponsors should file submissions in accordance with the Health Canada guidance document,* Preparation of Drug Submissions in the Electronic Common Technical Document (eCTD) Format.**

Sponsors are encouraged to request pre-submission meetings prior to filing a New Drug Submission for a vaccine. Early and ongoing consultation will help ensure that

regulatory requirements are met. These meetings also help Health Canada prepare for upcoming submissions. Sponsors should refer to the Health Canada guidance document,* Management of Drug Submissions *for instructions on how to request pre-submission meetings.

2. Guidelines for Preparation of an Application

This document provides guidance to industry for the preparation of submissions according to the format presented in the ICH CTD.

Each country has its own application licensing procedure and specific forms to comply with their National legislation. The minimum information to be submitted by the applicant has been harmonized by the PANDRH Working Group on Vaccines based on the ICH CTD format. This chapter describes how this format applies to the specific requirements for vaccines. Vaccines are always considered new products for licensing purposes.

Module 1. Administrative Information and Prescribing Information

The information requested in this module is specific to each country and is generally based on National legislation.

Sponsors that intend to file a New Drug Submission to Health Canada should refer to the most up-to-date version of Health Canada's Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format for the information that should be included in Module 1.

Module 2. Common Technical Document Summaries

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological); nonclinical and clinical information presented in modules 3, 4, and 5 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 3, 4, and 5.

Additional information for the preparation of this section can be found in ICH M4Q (R1), M4S (R2) and M4E (R1).

The information in module 2 should be presented in the following order:

2.1 Common Technical Document Table of Contents (Modules 2-5)

A general index should be included of the scientific information contained in modules 2 to 5.

2.2 CTD Introduction

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

2.3 Quality Overall 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 3 or in other modules of the submission. For example, if the submission describes more than one drug substance, manufacturer, dosage form, formulation, type of packaging, and/or strength, the applicant should summarize this information in the Quality Overall Summary (QOS) using a similar format as in the Module 3.2 Body of Data.

The format should be as follows:

Introduction

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It is important to note that the Drug Substance refers to the vaccine component or antigen, and the Drug Product refers to the final product.

2.3.S Drug Substance (Name, Manufacturer)

2.3.S.1 General Information (name, manufacturer)

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.3 Characterisation (name, manufacturer)

2.3.S.4 Control of Drug Substance (name, manufacturer)

2.3.S.5 Reference Standards or Materials (name, manufacturer)

2.3.S.6 Container Closure System (name, manufacturer)

2.3.S.7 Stability (name, manufacturer)

2.3.P Drug Product (Name, Dosage Form)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

2.3.P.2 Pharmaceutical Development (name, dosage form)

2.3.P.3 Manufacture (name, dosage form)

2.3.P.4 Control of Excipients (name, dosage form)

2.3.P.5 Control of Drug Product (name, dosage form)

2.3.P.6 Reference Standards or Materials (name, dosage form)

2.3.P.7 Container Closure System (name, dosage form)

2.3.P.8 Stability (name, dosage form)

2.3.A Appendices

2.3.A.1 Facilities and Equipment (name, manufacturer)

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

2.3.A.3 Excipients

2.3.R Regional Information

2.4 Nonclinical Overview

An integrated and critical assessment of the nonclinical evaluation of the vaccine should be provided.

The Nonclinical Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references

2.5 Clinical Overview

A succinct discussion and interpretation of the clinical data should be presented. The Clinical Overview should present the strengths and limitations of the clinical development program and study results, and analyse the benefits and risks of the vaccine in its intended conditions for use.

The format for the Clinical Overview should be as follows:

2.5.1 Product Development Rationale

A discussion of the rationale for the development of the vaccine should be presented.

2.5.2 Overview of Biopharmaceutics

Summary of bioanalytical methods used to assess the immunogenicity of the vaccine in clinical trials. Refer to guidelines provided for Module 5 below.

2.5.3 Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the pharmacodynamics (e.g. immunogenicity), information on mechanism of action and related in vitro data provided in Module 5 of the CTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. The analysis should emphasize unusual results and known or potential problems, or note the lack thereof.

2.5.4 Overview of Efficacy

A critical analysis of the clinical data pertinent to the efficacy of the vaccine in the intended population should be presented. The analyses should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information.

2.5.5 Overview of Safety

A concise critical analysis of the safety data should be presented noting how results support and justify the proposed prescribing information.

2.5.6 Benefits and Risks Conclusions

Integrate all of the conclusions reached in the previous sections about the efficacy and safety of the vaccine and provide an overall appraisal of the benefits and risks of its use.

2.5.7 Literature References

2.6 Nonclinical Written and Tabulated Summaries

The format for the Nonclinical Written and Tabulated Summaries should be as follows:

2.6.1 Introduction

An introduction to the vaccine and its proposed clinical use should be presented.

2.6.2 Pharmacology Written Summary

The format should be as follows:

2.6.2.1 Brief Summary

2.6.2.2 Primary Pharmacodynamics

2.6.2.3 Secondary Pharmacodynamics

2.6.2.4 Safety Pharmacology

2.6.2.5 Pharmacodynamic Drug Interactions

2.6.2.6 Discussion and Conclusions

2.6.2.7 Tables and Figures

2.6.3 Pharmacology Tabulated Summary

If applicable, summary tables for the pharmacology studies should be presented.

2.6.4 Pharmacokinetics Written Summary

This is generally not performed for vaccines. However, biodistribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors. The feasibility of such studies should be evaluated on a case-by-case basis. If applicable, the format for the written summary of pharmacokinetic studies should be as follows:

2.6.4.1 Brief Summary

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic Drug Interactions (nonclinical)

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and Figures

2.6.5 Pharmacokinetics Tabulated Summary

Pharmacokinetic studies are not generally performed for vaccines. However, for live attenuated vaccines (viral or bacterial including vaccine vectors) there are potential causes of clinically significant infections in the recipient or in contacts. Clinical study reports providing information on shedding, reversion characteristics and transmission to contacts should be provided here.

If applicable, summary tables for the pharmacokinetics studies should be presented.

2.6.6 Toxicology Written Summary

A written summary of toxicology studies should be presented. Refer to guidelines provided for Module 4 below. The format for the Toxicology Written Summary should be as follows:

2.6.6.1 Brief Summary

2.6.6.2 Single-Dose Toxicity

2.6.6.3 Repeat-Dose Toxicity

2.6.6.4 Genotoxicity

2.6.6.5 Carcinogenicity

2.6.6.6 Reproductive and Developmental Toxicity

2.6.6.7 Local Tolerance

2.6.6.8 Other Toxicity Studies

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

2.6.7 Toxicology Tabulated Summary

Summary tables for the toxicology studies should be presented.

2.7 Clinical Summary

A detailed, factual summary of all clinical data should be presented. This includes information provided in clinical study reports, information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and, post-marketing data for vaccines that have been marketed in other regions.

The format for the Clinical Summary should be as follows:

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

A summary of the bioanalytical assays used to assess vaccine immunogenicity in clinical trials should be provided. This section should also provide an overview of the scientific rationale, the criteria used for the selection of analytical methods, and the cut-off / threshold values applied. In addition, information on the performance characteristics of assays including the validation (e.g. linearity range, sensitivity, specificity) and quality control (e.g. accuracy and precision) should be included. This section should not include detailed information about individual studies. Refer to guidelines provided for Module 5 below. If applicable, the format of the summary is as follows:

2.7.1.1 Background and Overview

2.7.1.2 Summary of Results of Individual Studies

2.7.1.3 Comparison and Analyses of Results Across Studies

2.7.1.4 Appendix

2.7.2 Summary of Clinical Pharmacology Studies

For vaccines this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Refer to guidelines provided for Module 5 below. If applicable, the format of the summary should be as follows:

2.7.2.1 Background and Overview
2.7.2.2 Summary of Results of Individual Studies
2.7.2.3 Comparison and Analyses of Results across Studies
2.7.2.4 Special Studies
2.7.2.5 Appendix

2.7.3 Summary of Clinical Efficacy

The format of the Summary of Clinical Efficacy should be as follows:

2.7.3.1 Background and Overview of Clinical Efficacy

This section should present a description of the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought.

2.7.3.2 Summary of Results of Individual Studies

A tabular listing of all studies providing (or designed to provide) information relevant to vaccine efficacy should generally be provided, together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g. similar to an abstract for a journal article, and should describe critical design features and critical results.

2.7.3.3 Comparison and Analyses of Results Across Studies

Using text, figures, and tables as appropriate, a summary of all available data that characterise the efficacy of the vaccine should be presented. This summary should include analyses of all data, irrespective of their support for the overall conclusions and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified. The format of this section is:

2.7.3.3.1 Study Populations

2.7.3.2.2 Comparison of Efficacy Results of all Studies

2.7.3.3.3 Comparison of Results in Sub-populations

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

2.7.3.6 Appendix

2.7.4 Summary of Clinical Safety

A summary of data relevant to safety in the intended vaccine recipient population, integrating the results of individual clinical study reports as well as other relevant reports should be presented. The safety profile of the vaccine, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with the use of tables and figures.

The format of the Summary of Clinical Safety should be as follows:

2.7.4.1 Exposure to the Drug

2.7.4.1.3 Demographic and Other Characteristics of Study Population

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

2.7.4.2.2 Narratives

2.7.4.3 Clinical Laboratory Evaluations

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

2.7.4.5 Safety in Special Groups and Situations

2.7.4.6 Post-marketing Data

2.7.4.7 Appendix

2.7.5 Literature References

A list of references cited in the Clinical Summary should be provided.

2.7.6 Synopses of Individual Studies

This section should include the table entitled Listing of Clinical Studies, described in guidance for Module 5, followed by all individual study synopses organised in the same sequence as the study reports in Module 5.

Module 3. Quality

The Quality information submitted under Module 3 should be up-to-date, comprehensive, appropriately detailed, relevant, and to the extent sufficient to support the approval of a vaccine submission. A properly completed Module 3 will facilitate preparation of the Quality Overall Summary (QOS) and will expedite the submission review process.

For a vaccine containing more than one drug substance, the entire Module 3.2.S Drug Substance for one drug substance should be followed by the entire Module 3.2.S Drug Substance for the next drug substance and then followed by the entire 3.2.P Drug Product. The name of the Drug Substance should be included in the heading of all applicable sections and subsections to clearly distinguish the information for each Drug Substance.

For a vaccine with more than one dosage form or for a vaccine supplied in multiple components, e.g. lyophilized powder with a reconstitution diluent, the entire Module 3.2.P Drug Product for one component or dosage form should be followed by the entire Module 3.2.P Drug Product for the next component or dosage form. The name of the component or dosage form should be included in the headings of the corresponding Module 3 sections.

Additional information for the preparation of this section can be found in ICH M4Q (R1), as well as WHO recommendations for the production and control of specific vaccines and other relevant international regulatory guidelines.

3.1 Table of Contents of Module 3

3.2 Body of Data

3.2.S Drug Substance (Name, Manufacturer)

The information requested under this point should be supplied individually for each antigen in the vaccine.

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Trade and/or non-proprietary name of the drug substance. Based on the WHO or Pharmacopoeia requirements, as appropriate.

3.2.S.1.2 Structure (name, manufacturer)

Structural formula, molecular formula, and relative molecular mass (if applicable). The schematic primary sequence such as amino acid sequence indicating glycosylation sites or repeating units of polysaccharide indicating modification sites or other post-translational modifications and relative molecular mass should be provided, if applicable.

3.2.S.1.3 General Properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance, including immunological characteristics and other biological activity, if applicable.

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

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

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

A description of the manufacturing process. Submit a description of the manufacturing process that includes all of 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 manufacturing process showing all of the manufacturing steps, including intermediate processes.

- Batch(es) and Scale Definition: An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided. Since pooling may occur at more than one step, it may be more appropriate to describe the batch size and

scale under the respective step(s), both within the flow diagram(s) and in the detailed description.

- Cell culture and harvest: A description of the cell culture, seed culture and harvest from the original inoculum up to the last harvesting operation.

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

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

- Description of the conjugation process. Indicate when applicable and/or when a modification of drug substance is performed. Also include information on the origin and quality control of the starting material used to obtain the substance used as a protein carrier.

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

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

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

- Storage and shipping conditions. When applicable, describe the equipment used, areas and buildings (if pertinent) and the shipping and storage conditions for the drug substance.

3.2.S.2.3 Control of Materials (name, manufacturer)

General description of the starting materials. For each biological starting material used to obtain or extract the drug substance, 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 Banks Systems. Origin, identification, characterization, preparation method, analysis certificates, adventitious agents testing, stability, controls, and frequency of the tests, definition of the number of passes should be included. In the case of cell banks, demonstrate that the characteristics of the cells remain unaltered in the passes used in production and successively.

- Embryonated eggs. Information on their origin, identification, quality certificates should be provided.

- General description of the raw materials. Considering the raw materials used in the preparation process from which the drug substance 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.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

Identification of critical steps in-process and controls. Selection and justification of critical steps, starting from inoculation up to the production of the drug substance, defining the operational parameters to control during the critical stages, including quality specifications should be included.

Intermediates. Summary of the quality, control, and storage conditions of intermediates isolated during the process should be provided. Stability data supporting storage conditions of intermediates should be provided.

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

A summary of the process validation and evaluation studies should be provided.

Note: For submissions to Health Canada, both the summary of the validation studies as well as the actual validation reports should be provided.

Information should be sufficient to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate the selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification). The information provided should support the current manufacturing process proposed for commercial use, including data to demonstrate consistency in yield and production, and degree of purity. If an adjuvant is added to the drug substance, validation data should be submitted to demonstrate consistency of manufacturing of the drug substance (e.g. dispersion, pre-determined particle size). Furthermore, for an alum-containing vaccine, study data to demonstrate consistency of adsorption of the drug substance to the adjuvant should be submitted.

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced or provided as part of justifying the selection of critical process controls and acceptance criteria.

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number (and subsequent drug product batch numbers), manufacturing date, scale, and use (e.g. stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality (e.g. biological activity, impurity profile) of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on the quality of the drug substance (see Q6B for additional guidance). A discussion of the data, a justification for selection of the tests and assessment of the results should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. A cross-reference to the location of these studies in other sections of Module 3 (e.g. Stability, Control of Drug Substance or Drug Product) and/or in other modules of the submission should be included.

A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency should also be provided.

3.2.S.3 Characterisation (name, manufacturer)

Present data to determine the structure and physicochemical, immunological, and biological characteristics of the drug substance.

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

For desired product and product-related substances, details should be provided, if applicable, on primary sequence, secondary and

higher-order structure, post-translational forms (e.g. glycoforms), biological activity, purity, and immunochemical/immunogenicity properties, when relevant. In addition, depending on the type of vaccine, this may include active or passive immunization studies and challenge studies as appropriate.

A summarized description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data, such as primary and higher order structure and biological activity, should also be provided.

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided. All potential impurities, including process related impurities and degradation products for purified vaccines such as polysaccharide/protein or synthetic peptide vaccines, arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches.

The actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported, for example, using a summary table.

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification. A rationale for excluding any impurity test(s) from routine release testing due to trace levels should also be provided, where applicable.

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification for the drug substance should be provided. For example, the specification could be presented using a table with the specification reference number, specification approval date, test parameter(s), method type, method code, source, and acceptance limit(s) at release, shelf-life or for both.

3.2.S.4.2 Analytical Procedures (name, manufacturer)

The analytical procedures used for testing the drug substance should be provided.

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

3.2.S.4.4 Batch Analysis (name, manufacturer)

Description of batches and results of batch analyses should be provided. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use.

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specification should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

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

3.2.S.6 Container Closure System (name, manufacturer)

Full description of the packaging and container closure system in which the drug substance 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. This description should include the information appearing on the labels.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

665 3.2.S.7 Stability (name, manufacturer)

666 *3.2.S.7.1 Stability Summary and Conclusions (name,*
667 *manufacturer)*

668 Should include the study conditions, including all of the storage
669 conditions (temperature, humidity, light) in which the vaccine is
670 evaluated, analytical method, specifications, summary of results,
671 and conclusions.

672 *3.2.S.7.2 Post-approval Stability Protocol and Stability*
673 *Commitment (name, manufacturer)*

674 It refers to the continuation of the stability study, including the
675 number of lots to be included in the study each year and the
676 tests to be performed.

677 *3.2.S.7.3 Stability Data (name, manufacturer)*

678 Should include complete data from each batch evaluated during
679 stability studies.

680 3.2.P Drug Product (Name, Dosage Form)

681 3.2.P.1 Description and Composition of the Drug Product (name, dosage
682 form)

683 This should include a description of the drug product, its composition,
684 listing each of the components, drug substance(s), adjuvant, preservatives,
685 stabilizers, and excipients, stating the function of each of them. For
686 lyophilized products, also include a description of the diluents and the
687 container closure system employed for the diluents.

688 3.2.P.2 Pharmaceutical Development (name, dosage form)

689 Information on the studies performed to establish the dosage form,
690 formulation, manufacturing process, and the container closure system used
691 for the final product. The studies described in this point are different from
692 the routine quality control tests performed in accordance with the product
693 specifications. The following aspects should be included:

694

695

3.2.P.2.1 Components of the Drug Product (name, dosage form)

Compatibility of the drug substance with the rest of the components in the drug product should be discussed, including adjuvant, preservative, stabilizers, as applicable.

3.2.P.2.2 Drug Product (name, dosage form)

Development of the formulation considering the proposed route of administration. Physicochemical and biological properties of the product, indicating the relevant parameters for developing the drug product should be included. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

Description of the selection and optimization of the manufacturing process, particularly for critical aspects. Significant differences between the manufacturing process used to produce batches for pivotal clinical trials or primary stability studies and the proposed commercial manufacturing process should be discussed.

3.2.P.2.4 Container Closure System (name, dosage form)

Full description of the packaging and container closure system. The information should include identification of all the materials that constitute the container closure system and their specifications. This description should include the information appearing on the labels.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug product, including sorption to container and leaching, and/or safety of materials of construction.

3.2.P.2.5 Microbiological Attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of

the container closure system to prevent microbial contamination should be addressed.

3.2.P.2.6 Compatibility (name, dosage form)

The compatibility of the drug product with reconstitution diluents (e.g. precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life at the recommended storage temperature and at the likely extremes of concentration.

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

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

3.2.P.3.2 Batch Formula (name, dosage form)

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

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

- Flow chart of manufacturing process. Showing all of the steps in the process and indicating the points at which the material enters the process, identifying the critical steps and control points in the process, intermediate products, and final product.

- Batch and Scale Definition. An explanation of the batch numbering system and scale at each stage of manufacture (e.g. filing, lyophilisation, and packaging).

- Formulation process. Description of the formulation process, the in-process controls, acceptance criteria and the critical steps identified. Information regarding any pooling of bulks or intermediates should be provided.

- Filling process. Description of the filling process, the process controls, acceptance criteria, and the critical steps identified.

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

- Storage and shipping conditions. When applicable, describe the equipment used, areas and buildings (if pertinent), and the shipping and storage conditions for the drug product.

- Description of procedures to guarantee 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 of 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.P.3.4 Control of Critical Steps and Intermediates (name, dosage form)

Identification of critical steps in the process and controls. The selection and justification of critical steps in the drug product manufacturing process should be included. Tests and acceptance criteria developed to identify the critical steps in the manufacturing process and how they were controlled should be described.

Intermediates. Information on the quality and control of intermediates isolated during the process should be provided.

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

A summary of the process validation and evaluation studies should be provided.

In Canada, the actual validation reports may be requested during the review process. If requested, the reports should be filed within this section.

The information provided should support the current manufacturing process proposed for commercial use, including in-process test results and data from relevant manufacturing batches to demonstrate consistency in yield and production, and degree of purity. A summary of the validation study for the extent of reuse and integrity of membranes should be provided, including data to demonstrate consistency in the quality and safety of the drug product.

The suitability of any proposed reprocessing procedures and the criteria for the reprocessing of any intermediate or the drug product should be discussed.

If adjuvants are added to the drug product, information and data from the adsorption and desorption study should be submitted, if applicable.

It is also necessary to provide information on the viral safety of the product, when applicable.

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

Provide information on the specifications for all of the substances employed in the formulation of the drug product that are different from the drug substance.

3.2.P.4.2 Analytical Procedures (name, dosage form)

Description or literature of reference of the methods used to control these substances.

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

Include the procedures used to control substances employed in formulating the final product.

3.2.P.4.4 Justification of Specifications (name, dosage form)

Include information about all substances used in formulating the final product.

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

Provide information on the source, origin, description of the quality tests performed, specifications, determination of adventitious agents, and viral safety data.

3.2.P.4.6 Novel Excipients (name, dosage form)

For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a vaccine for human use or for a new route of administration, all information on the manufacture, characterisation, and control should be submitted under 3.2.A.3 according to the drug substance and/or drug product CTD format, with a cross-reference to 3.2.A.3 under this section. Cross-references to nonclinical studies (Module 4) and clinical studies (Module 5) supporting the safety of a novel excipient should also be provided under this section.

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

Indicate the specifications for the drug product.

3.2.P.5.2 Analytical Procedures (name, dosage form)

Information on the analytical procedures used for quality control of the drug product. Non-pharmacopeia methods, summaries or references are not accepted. Additional information could be requested.

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

Include information on the validation of the analytical procedures for the drug product, including experimental data.

866 *3.2.P.5.4 Batch Analyses (name, dosage form)*

867 The production and control protocols for at least three lots of
868 drug product should be submitted, including an analysis of the
869 results for those lots in terms of production consistency.

870 *3.2.P.5.5 Characterisation of Impurities (name, dosage form)*

871 As applicable, depending on the method used to manufacture the
872 vaccine submitted for licensing.

873 *3.2.P.5.6 Justification of Specification(s) (name, dosage form)*

874 Provide justification of the specifications proposed for the drug
875 product.

876 3.2.P.6 Reference Standards or Materials (name, dosage form)
877
878 Provide information on the reference standards and/or materials used in
879 the tests to control the drug product.

880 3.2.P.7 Container Closure System (name, dosage form)

881 Describe in detail the type and form of container closure systems of the
882 drug product, including the materials of which they are made and quality
883 specifications.

884 3.2.P.8 Stability (name, dosage form)

885 *3.2.P.8.1 Stability Summary and Conclusion (name, dosage*
886 *form)*

887 Submit the stability study that complies with each country's
888 legislation, including the study protocol, specifications, analytical
889 methods, detailed description of the container closure system for
890 the product evaluated, storage conditions (temperature and relative
891 humidity), summary of results for at least three lots of drug product
892 prepared from different lots of drug substance, conclusions, and
893 proposed validity period. The stability studies should be signed by
894 the professional in charge of the study.
895
896 It is important to provide additional studies on the stability of
897 the vaccine in intermediate stages in the manufacturing process
898 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.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

Include the stability program or stability commitment to be carried out once the vaccine is on 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.

3.2.P.8.3 Stability Data (name, dosage form)

Include the complete results of each lot evaluated during stability studies.

If applicable, forced degradation studies should be filed within this section.

3.2.A Appendices

Some of the appendices may be considered optional by some authorities.

3.2.A.1 Facilities and Equipment (name, manufacturer)

This section should be included in vaccine submissions to Health Canada.

A 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 should be provided. Also, submit information on all of the products prepared and/or handled in the same areas as the product submitted for licensing. Describe the procedures to avoid cross-contamination of areas and equipment.

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

This section should be included in vaccine submissions to Health Canada.

Additional, detailed information on evaluation of the safety of the product in relation to adventitious agents of both viral and non-viral origin should be submitted.

3.2.A.3 Excipients

This appendix is *required* where applicable.

Novel Excipients - For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a vaccine for human use or for a new route of administration, information to support the quality, safety, and suitability for use should be provided in this appendix. This section should be submitted according to the drug substance and/or drug product CTD format described in this document along with cross-references to nonclinical studies (Module 4) and clinical studies (Module 5) supporting the safety of a novel excipient.

Other Excipients - Any extensive drug substance and/or drug product information which is necessary to support the quality, safety, suitability for use, and 'approvability' of any (non-novel) non-compendial excipient, and/or any excipient of human or animal origin, should also be provided in this section.

3.2.R Regional Information

Any additional drug substance and/or drug product information specific to each region should be provided in this section of the application. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

3.2.R.1 Production Documentation

3.2.R.1.1 Executed Batch Records (name, dosage form, manufacturer)

Executed batch records for 3-5 consecutively manufactured or consistency drug product lots from each production site or facility should be provided. ***In Canada, these should be made available upon request.***

3.2.R.2 Medical Devices (name, dosage form)

For a vaccine supplied with a medical device, a description of the device(s), including its application, manufacturer, and confirmation that it has been notified or approved for use by Health Canada should be provided.

3.2.R.3 Lot Release Documentation (name, dosage form)

The proposed test protocol format for the release package, including Certificate of Analysis for the drug substance or drug product, and safety certification for any biological excipient used, if applicable (e.g. a Plasma Certificate), should be provided. The documentation should include the name and title of the delegate with signing authority for lot release.

3.2.R.4 Yearly Biologic Product Report

In Canada, the Yearly Biologic Product Report (YBPR) should be filed in this section. Sponsors should refer to the Health Canada Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs for more information.

3.3 Literature References

Module 4. Nonclinical Study Reports

Nonclinical studies should comply with the WHO's *Guidelines on Nonclinical Evaluation of Vaccines*, WHO Technical Report Series No. 927, 2005, or the most recent version. In addition, vaccines containing adjuvants should comply with the WHO *Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines.* Additional information for the preparation of this section can be found in ICH M4S (R2).

4.1 Table of Contents of Module 4

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

A pharmacodynamic study for a vaccine product is generally conducted to evaluate the immunogenicity of the vaccine or, when animal models are available, the capacity of a vaccine to confer protection. In addition, a pharmacodynamic study may also extend to include the pharmacology of an adjuvanted vaccine to provide evidence for the need for the adjuvant.[1]

4.2.1.2 Secondary Pharmacodynamics

Generally not performed for vaccines.

4.2.1.3 Safety Pharmacology

The purpose of a safety pharmacology study is to investigate the effects of the candidate vaccine on vital functions. Although not usually required for vaccines, safety pharmacology studies may be recommended by the NRA in some cases. For example, if data from nonclinical and/or human clinical studies suggest that the adjuvanted vaccine may affect physiological functions (e.g. central nervous, respiratory, and cardiovascular systems, renal functions and body temperature) other than the immune system, safety pharmacology studies should be incorporated into the safety assessment program.[1]

4.2.1.4 Pharmacodynamic Drug Interactions

Generally not performed for vaccines.

4.2.2 Pharmacokinetics

Generally not performed for vaccines; however, biodistribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors. The feasibility of such studies should be evaluated on a case-by-case basis.

Where pharmacokinetic studies have been performed, the study reports should be provided in the relevant sections below:

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity

Single dose toxicity studies on the final formulated vaccine product, which are applicable to small molecule chemical drugs, are usually not needed for vaccines. Acute effects of administering the vaccine can also be monitored in repeated dose toxicity studies if they are adequately designed (e.g. evaluation is conducted after the first administration). Alternatively, acute effects can be assessed in a single dose design as part of a local tolerance study.[1]

4.2.3.2 Repeat-Dose Toxicity

Information should be included to justify the study design (e.g. number of animals per group), animal model used (e.g. animal species, age, dose, route of administration) and the parameters monitored.

4.2.3.3 Genotoxicity

Generally not performed for vaccines. However, it may be required if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity.

Where genotoxicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including toxicokinetics)

Generally not performed for vaccines. However, it may be required if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity.

Where carcinogenicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.3.4.1 Long-term studies (not included in repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (not included under

repeat-dose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, if the target population for the vaccine includes pregnant women and women of child-bearing potential, developmental toxicity studies should be considered unless a scientific and clinically sound argument is put forward by the manufacturer to show that conducting such studies is unnecessary.[2]

Where reproductive and developmental toxicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

4.2.3.6 Local Tolerance

The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study.[2]

4.2.3.7 Other Toxicity Studies (if available)

Where other toxicity studies have been performed the reports should be provided in the relevant sections below:

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other studies

4.3 Literature References

Module 5. Clinical Study Reports

Sponsors may refer to the WHO *Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations* (WHO Technical Report Series, 924, 2004 or the most recent version). The WHO recommendations applicable to the specific vaccine should also be considered as well as other national and international regulatory guidelines. Additional information for the preparation of this section can be found in ICH M4E (R1).

Clinical trials in humans are generally classified into three Phases: Phase I, Phase II and Phase III and, in certain countries, formal regulatory approval is required to undertake any of these studies. This approval takes different forms in different countries (e.g. Investigational New Drug Application (IND) in the United States and Clinical Trial Certificate or Clinical Trial Exemption (CTX) in the United Kingdom). This is in addition to ethical clearance which is required for clinical trials in all countries. All studies of human subjects require proper ethical review, in accordance with the Declaration of Helsinki.

A Clinical Trial Application (CTA) is required for studies conducted in Canada. Sponsors should refer to Part C, Division 5 of the Food and Drug Regulations and Health Canada's Guidance for Clinical Trial Sponsors: Clinical Trial Applications for more information. Before submitting a CTA, sponsors are encouraged to request a pre-CTA meeting to seek input from Health Canada on scientific, quality, clinical, and other regulatory issues at an appropriate stage of product development.

The Phase I clinical studies carry out initial testing of a vaccine in small numbers (e.g. 20) of healthy adults to test the properties of a vaccine, its tolerability, and, if appropriate, clinical laboratory and pharmacological parameters. Phase I studies are primarily concerned with safety.

Phase II studies involve larger numbers of subjects and are intended to provide preliminary information about a vaccine's ability to produce its desired effect (usually immunogenicity) in the target population and its general safety.

To fully assess the protective efficacy and safety of a vaccine, extensive Phase III trials are required. The Phase III clinical trial is the pivotal study on which the decision on

whether to grant the licence is based and sufficient data has to be obtained to demonstrate that a new product is safe and effective for the purpose intended.

By the beginning of the Phase III stage of development, a vaccine should have been fully characterized and the final manufacturing process, specifications and batch release testing procedures should have been established. An application for market authorization may be submitted to an NRA on the basis of the data from Phase III testing and, if approved, the vaccine then becomes commercially available in that particular country.

If a product contains or consists of genetically modified organisms, an environmental risk assessment should also be undertaken and approved by the appropriate agency.
The structure of the clinical development programme must be tailored to the type of vaccine and the antigenic content. For example, the clinical evaluation of a vaccine that contains only novel antigen(s) may of necessity be very different from that of a vaccine that contains one or more previously evaluated antigens. Such factors also influence whether clinical protection trials will be required, whether or not they are feasible, or whether an approval may reasonably be based on immunogenicity data. In all instances, it is the obligation of the applicant to justify the content and structure of the clinical development programme. Pre-submission meetings with regulatory authorities may assist in ensuring that the content of the final data package is likely to be acceptable.

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided (e.g. type of study, study identifier, location of study report in the application, study objectives, study design and type of control, dosage regimen, route of administration, number and type of subjects, study status). The sequence in which the studies are listed should follow the sequence described in section 5.3 below.

5.3 Clinical Study Reports

Clinical study reports should be provided in the relevant sections below. Additional information on the structure and content of the Clinical Study Report can be found in ICH M4E (R1).

5.3.1 Reports of Biopharmaceutic Studies

Biopharmaceutic studies are not generally performed for vaccines; however, section 5.3.1.4 is required when immunogenicity studies are conducted.

5.3.1.1 Bioavailability Study Reports

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

5.3.1.3 In vitro - In vivo Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

This section is required for vaccines and should include validation reports of all assays used to assess vaccine immunogenicity in clinical trials.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

Not generally performed for vaccines.

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

Not generally performed for vaccines.

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic Studies

For vaccines, this section should provide the reports of the immunogenicity studies conducted to support the selection of dose, dosage schedule, and formulation of the final product. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Section 5.3.5.

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

Reports of all clinical studies conducted to assess the efficacy and safety of the vaccine conducted by the sponsor (or otherwise available), including all completed and all ongoing studies of the vaccine in proposed and non-proposed indications, should be provided in the relevant sections below.

For live attenuated vaccines (viral or bacterial, including vaccine vectors) there are potential causes of clinically significant infections in the recipient or in contacts. Clinical study reports providing information on shedding, reversion characteristics, and transmission to contacts should be provided in this section.

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Controlled clinical study reports should be sequenced by type of control in the following order:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control (not generally performed for vaccines)
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies, e.g. reports of open label safety studies.

5.3.5.3 Reports of Analyses of Data from More than One Study

Reports of formal integrated analyses, meta-analyses and bridging analyses.

5.3.5.4 Other Study Reports

This section can include the following:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication

- Reports of ongoing studies
- Development Safety Update Reports

5.3.6 Reports of Post-Marketing Experience

Relevant post-marketing studies or information (including all significant safety observations) should be included here.

In Canada, Periodic Benefit Risk Evaluation Reports (PBRERs) should be included in Section 5.3.6.

5.3.7 Case Report Forms and Individual Patient Listings (when submitted)

Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline should be placed in this section, when submitted, in the same order as the clinical study reports and indexed by study.

In Canada, case report forms should be available but only submitted upon request.

5.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

3. Contact Information

Canadian submission inquiries should be directed to - (http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/bgtd-pbtg-ora-bar-eng.php):
Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Canada
Phone: 613-957-1722
Fax: 613-946-9520
Email: bgtd.ora@hc-sc.gc.ca

Reference Documents

1. Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines. Geneva, World Health Organization, 2013, (WHO Technical Report Series, No. 987), Annex 2.

2. WHO guidelines on nonclinical evaluation of vaccines. In: WHO Expert Committee on Biological Standardization. Fifty-fourth report. Geneva, World Health Organization, 2005 (WHO Technical Report Series No. 927), Annex 1.

3. Guidelines on clinical evaluation of vaccines: regulatory expectations. In: WHO Expert Committee on Biological Standardization. Fifty-second report. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924), Annex 1.

4. The ICH M4 guidelines adopted by Health Canada can be obtained from the ICH website (www.ich.org) :

M4

Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use

M4Q (R1)

The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality

- Quality Overall Summary of Module 2
- Module 3: Quality

M4S (R2)

The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety

- Non-Clinical Overview and Non-Clinical Summaries of Module 2
- Organization of Module 4

M4E (R1)

The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy

- Clinical Overview and Clinical Summary of Module 2
- Module 5: Clinical Study Reports