GUIDELINES FOR REGISTRATION OF HUMAN VACCINES

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Safe Drugs Save Lives

Citation

These guidelines shall be cited as the *"Professional Guidelines on Registration of Human Vaccines, Doc. No. PAR/GDL/021, Revision No.: 0"*

Adoption and Approval of these professional Guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional Guidelines on **Registration of Human Vaccines,** Doc. No. PAR/GDL/021, Revision No.:0, made this 10th day of October, 2019, that take effect on 14th October 2019.

Signature

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TABLE OF CONTENTS

INTRODUCTION

The Uganda National Drug Authority has a role to ensure that vaccines coming onto the market meet the quality, safety, and efficacy standards for clinical use. The Authority should exercise adequate regulatory oversight over vaccines because they are usually given to very large numbers of healthy individuals. It should be noted that vaccines differ from chemical drugs because of the biological nature of the source materials (such as those derived from microorganisms), the biological methods used to test them, the lack of a classical pharmacokinetic measurable mode of action and because they are highly complex substances. Some vaccines consist of live microorganisms suitably changed or attenuated to ensure that they no longer produce disease but can still produce a suitable immune response. Special expertise and procedures are needed for their manufacture, control, and regulation.

Before a vaccine is considered for approval, sufficient scientific and clinical evidence must be collected to show that it is safe, efficacious and of suitable quality. This scientific evidence includes results from human clinical trials and for acceptance; it should be evident that the benefits of the vaccine outweigh any risks associated.

When all above is in place, additional mechanisms like: risk-based lot release program, assessment of post-market changes, post-market surveillance for compliance verifications as well as investigation of potential health hazards and other violations should be implemented.

Furthermore, regular inspections of manufacturers, packagers/labellers, testing laboratories, importers, distributors and wholesalers of vaccines may be conducted to ensure that they comply with Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP)

These guidelines prescribe data, which is required to be submitted to NDA to demonstrate the safety, efficacy and quality of vaccines being applied for market authorization. The guidelines also describe the format (CTD) in which dossiers should be presented in support of the application. According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements, which is region specific. The Overviews and Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5, respectively.

These guidelines should be read in conjunction with other international guidelines on quality, safety and efficacy of vaccines as cited in this guideline, namely the World Health Organization (WHO), European Medicines Agency (EMA) and International Conference of Harmonization (ICH).

Objective

The objective of this guideline is to streamline the registration process of vaccines in Uganda for human use.

Policy

These guidelines are developed in accordance with the National Drug Policy and Authority Act Cap 206, Section 35 and section 4 of the National Drug Policy and Authority (Registration) Regulations, 2014.

Scope

These guidelines are intended to provide general considerations and guidance on content and format for required information for regulatory submission of vaccines for the purpose of marketing authorization in Uganda. Technical and product-specific guidance are referenced in this document.

The vaccine categories include: -

(a) Microorganisms or toxins inactivated by chemical or physical means that retain appropriate immunogenic properties;

(b) Living microorganisms that have been attenuated whilst retaining immunogenic properties;

(c) Antigens extracted from microorganisms, secreted by them or produced by recombinant DNA technology; or

(d) Antigens produced by chemical synthesis in vitro including chemically conjugated or modified natural antigen.

(e) Inactivated antigens or toxins with enhanced immunogenicity by addition of adjuvants.

The principles expressed in this document may also apply to combined vaccines that are not explicitly mentioned.

ABBREVIATIONS AND ACRONYMS

CTD - Common Technical Documents (CTD)
EAC - East African Community
EMA - European Medicines Agency
ICH - International Council on Harmonization of Technical Requirements for Registration of Human Medicinal Products
GMP - Good Manufacturing Practices
HIV - Human Immunodeficiency Virus
MCB - Master Cell Bank
NOAD - New Onset Autoimmune Disease
NOCD - New Onset Chronic Disease
SDRAs - Stringent Drug Regulatory Authorities
SOP - Standard Operating Procedure
TSE - Transmissible spongiform encephalopathies
VVM - Vaccine Vial Monitor
WHO - World Health Organization

GLOSSARY

For the purposes of these guidelines, the following definitions shall apply:

"Adjuvant" means a component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses.

"Adverse Events Following Immunization" means any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

"Combination Vaccine" means a combination vaccine consists of two or more live organisms, inactivated organisms or purified antigens combined either by the manufacturer or mixed immediately before administration. (Refer to FDA Guidance for Industry for the Evaluation of Combination vaccines for Preventable Diseases: Production, Testing and Clinical Studies)

"Batch (or lot)" means a defined quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. (Refer to ICH Topic Q 7 Good Manufacturing Practice for Active Pharmaceutical Ingredients)

"Follow-on manufacturer" means a new manufacturer of vaccine that has been granted market authorization by SDRA(s).

"Immunological product" is a medicinal product containing an immunogenic substance. Immunological products include vaccines, immunoglobulins and antisera and in vitro diagnostic antigens

"Immunogenic Substance" is the unformulated active substance which may be subsequently formulated with excipients to produce the medicinal product. Immunogenic substance may be whole bacterial cells, viruses, or parasites (live or killed), split bacterial cells, viruses, or parasites, crude or purified antigens isolated from killed or living cells; crude or purified antigens secreted from living cells, recombinant or synthetic carbohydrate, protein or peptide antigens, polynucleotides (as in plasmid DNA vaccines) or conjugates.

"Manufacturer" means a natural or legal person with responsibility for manufacturing of a medicinal product or Immunogenic substance.

"Master Cell Bank (MCB)" means an aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB unless justified.

"Master Virus Seed (MVS)" is a viral seed of a selected vaccine virus from which all future vaccine production will be derived, either directly, or via Working Virus Seeds.

"**Officially recognized pharmacopoeia (or compendium)"** is the official recognized pharmacopoeias by the Authority. They include the current version of the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), The International Pharmacopoeia (Ph. Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP)

"Ongoing stability study" means the study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the immunogenic substance or confirm or extend the shelf-life of the medicinal product.(Refer to WHO Glossary of terms)

"Pilot Plant Scale" is the production of a recombinant protein by a procedure fully representative of and simulating that to be applied on a full commercial manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

"Pilot-scale batch" is a batch of an immunogenic substance or medicinal product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified. (Refer to WHO Glossary of terms)

"Primary batch" is a batch of an immunogenic substance or medicinal product used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. (Refer to WHO Glossary of terms)

"Production batch" is a batch of an immunogenic substance or medicinal product manufactured at production scale by using production equipment in a production facility as specified in the application.

"Vaccines" are a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease. (Refer to Guidelines on Stability Evaluation of Vaccines)

"Vaccine Vial Monitor (VVM)" is a heat-sensitive label attached to vaccine vials which gradually and irreversibly changes colour, from light to dark, as the vaccine is exposed to heat. It warns the health worker as to when a vial of a vaccine should be discarded because the vaccine is likely to have been degraded by exposure to heat.

"Working Cell Bank (WCB)" is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

"Working Virus Seed (WVS)" is a viral seed derived by propagation of virus from the MVS under defined conditions and used to initiate production cell cultures lot-by-lot.

1.0 MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments and overseas evaluation reports), as needed.

Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes. Official language is English as a mandatory language for all medicines.

For further guidance on submission procedure refer to NDA Guidelines on Submission of Documentation for Marketing Authorisation of a Pharmaceutical Product for Human Use

1.1 Cover letter

Applicants should include a cover letter with all applications. A copy of the letter should be placed at the beginning of Module 1. The applicant shall sign the cover letter.

1.2 Comprehensive table of contents for all modules

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module. In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents.

1.3 Application form

An application to register a medicinal product for human use must be accompanied by a completed application form (Appendix I). The application form should be dully filled with relevant information and attachments, dated, signed and stamped appropriately.

1.4 Product information

Provide copies of summary of product characteristics, labels, package inserts and any information intended for distribution with the product to the patient.

1.4.1 Summary of product characteristics (SmPC)

The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.

For more guidance refer to NDA Guidelines (Doc.No.PAR/GDL/004) on Format and Content of summary of product characteristics for pharmaceutical products.

1.4.2 Primary package label

Submit the label proposed for the product's primary container, which should provide the following information as a minimum:

a) Proprietary, commercial or trade name

b) Non-proprietary name

c) Pharmaceutical form

d) Concentration

e) Volume/content, if applicable

f) Number of doses per vial (for multi-dose presentations)

g) Route of administration

h) Storage conditions (for multi-dose presentations include storage conditions after initial opening)

i) Lot number

j) Manufacturing date

k) Expiry date

l) Name and Physical address of manufacturing site

m) Vaccine Vial Monitor (if applicable)

Note: The manufacturing date, physical address of the manufacturing site and storage conditions may be omitted on the primary container due to lack of space. The name of the manufacturer may be substituted with a trademark or other symbols. However, all these details should appear in full on the secondary packaging.

1.4.3 Secondary Package Label

Include the text proposed for the product's secondary packaging, which should provide the following information as a minimum:

a) Proprietary, commercial or trade name
b) Non-proprietary name and standard used
c) Pharmaceutical form
d) Concentration
e) Content/volume
f) Number of doses per vial (for multi-dose presentations)
g) Route of administration
h) Storage conditions for multi-dose presentations including storage conditions after initial opening
i) Lot number
j) Manufacturing date
k) Expiry date
l) Shelf life after first opening the container/in use shelf life
m) Physical address of manufacturing site

1.4.4 Package insert

The Package insert shall be drawn up in accordance with the SmPC. The package insert shall contain the following information as a minimum:

a) Proprietary, commercial or trade name
b) Non-proprietary or common name
c) Pharmaceutical form
d) Concentration, potency, or viral titre
e) Content/Volume of the unit pack
f) Volume per dose
g) Number of doses per vial (for multi-dose presentations)

h) Composition
i) Excipients including Preservatives
j) Cell substrate
k) Route of administration
l) Indications
m) Immunization plan
n) Proper use
o) Precautions
p) Warnings
q) Adverse Events
r) Contraindications
s) Use during pregnancy and breast feeding
t) Storage of the product/storage conditions for multi-dose presentations include storage conditions after initial opening
u) Name and address of the manufacturer of the finished product
v) Name and address of the company responsible for packaging.
w) Description of vaccine vial monitor stages (if applicable)

For templates of package inserts for specific type vaccines, refer to “WHO Model inserts”

1.4.5 Mock-up and specimens

If the product applicant has a specimen or mock-up of the sample(s) presentation of the medicine available at the time of initial application, it should be included in Module 1.4.5.
The purpose of this is to provide an example of the product, including accessories, if any, to verify that they correspond to what is described for the characteristics of the product under evaluation.

1.5 Information about the experts

A declaration should be sent signed by each of the experts who performed the product evaluation from the stand point 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.

A sample of declaration form is provided as Appendix II.

1.6 Certificate of Good Manufacturing Practices (GMP)

Provide certificate of GMP compliance from a competent drug authority or SDRA. This should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the finished immunological product, immunological substance(s), the diluents, and those responsible for labelling and packaging the finished immunological product.

1.7 Good Clinical Practice (GCP) and/or Good Laboratory Practice (GLP)

Provide evidence such as accredited certificate for GCP or GLP for the sites participating in the clinical studies

1.8 Regulatory Status

1.8.1 Registration status from countries with Stringent Drug Regulatory Authorities (SDRAs)

Provide registration status of the vaccine applied for registration in the countries with SDRAs and attach evidence(s) for the same (for example approval letters, rejection letters, withdraw letters, etc.).

1.8.2 Registration status in EAC Partner States

Provide registration status of the vaccine applied for registration in the EAC region and attach evidence(s) for the same.

1.8.3 List of countries in which a similar application has been submitted

The applicant should provide, in Module 1.8.3 of the dossier, a list of countries in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case.

1.8.4 Statement on whether an application for the product has been previously rejected, withdrawn or repeatedly deferred in the EAC Partner States

Applicant must declare whether a marketing application for the vaccine has been rejected prior to submission of the application in Uganda. If the vaccine has been rejected, repeatedly deferred, withdrawn or suspended then reasons must be stated.

1.9 Manufacturing and Marketing authorization

Submit a Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production. If available, evidence for prequalification of vaccine by WHO should be submitted.

1.10 Product samples

A minimum of two samples of each pack size applied for registration should be submitted together with the application. The samples should be provided in the form in which it shall appear on the market for physical evaluation. Where justified, artwork and pictures of the sample may be submitted.

1.11 Authorization of an agent in Uganda

Letter issued by the applicant authorizing the company to represent it and market the product in Uganda.

1.12 Lot release certificate

Provide 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.

1.13 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 product submitted for market authorization. These protocols are published in the WHO's Technical Report Series. For novel products 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. This should be presented in section 3.2.R.

1.14 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 or package insert.

2.0 MODULE 2: OVERVIEWS AND 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 product, 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. The information in module 2 should be presented in the following order:

2.1 Table of contents

An index should be included of the scientific information contained in modules 2

2.2 Introduction

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

2.3 Quality Overall Summary (QOS)

A general summary of the quality of the product 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 registration document.

This section should follow format as specified in the Quality Overall Summary template (Appendix III).

2.4 Overview and summary 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. Overview and summary of the results of the pharmacological, pharmacokinetic, and toxicological tests on animals and/or *in vitro* studies should be presented. The data should be presented as a written and tabulated summary, in the following order:

a) Introduction

b) Written pharmacological summary

c) Tabulated pharmacological summary

d) Written pharmacokinetic summary (when appropriate)

e) Tabulated pharmacokinetic summary (when appropriate)

f) Written toxicological summary

g) Tabulated toxicological summary

2.5 Overview and summary of the clinical studies

This section should include a critical analysis of the clinical results included in the clinical summary and in module 5. Information should include a summary of the clinical development of the product, the design of the pivotal studies, and the decisions related to the clinical studies and their performance and it should include an overview of the clinical conclusions and an evaluation of the risks/benefits in relation to the results of the clinical studies and justification of the proposed dosages. All the data related to efficacy/effectiveness and safety assessed through the development of the product should be summarized in this section as well as any study limitations. Summaries should include of all the clinical studies performed and synopsis of each study.

The data should be presented in a written and tabulated summary in the following order:

a) Introduction

b) Detailed discussion of the development of the product

c) Overview of immunogenicity

d) Overview of the efficacy

e) Overview of the safety

f) Conclusions and risk/benefit analysis

g) Bibliography

3.0 MODULE 3: QUALITY (CHEMISTRY, MANUFACTURING AND CONTROLS)

3.1 Table of contents of module 3

3.2.S Immunogenic substances

The information requested under this section should be provided individually for each immunogenic substance in the vaccine.

Production of immunogenic substance, whether by fermentation, cultivation, isolation, or synthesis, usually starts with biological raw materials. Subsequent steps of the procedure involve preparation, characterization and purification of intermediates eventually resulting in the immunogenic substance.

The quality and purity of the immunogenic substance cannot be assured solely by downstream testing, but depends on proper control of the manufacturing processes. Proper control and attainment of minimal levels of impurities depend on:

a) Appropriate quality and purity of the starting materials, including the seed lot system, cell banks and reagents;

b) Establishment and use of in-process controls for intermediates;

c) Consistent adherence to validated process procedures; and

d) Adequacy of the final (release) control testing of the immunogenic substance

3.2.S.1 General Information, starting materials and raw materials

This section should contain information on the source materials: source materials include any component / unformulated immunogenic substance used in the manufacture of the immunogenic product (e.g. microorganisms, cells/ cell substrate, immunogen) their specifications and the tests used to demonstrate compliance with the Specifications. The following information should be provided:

3.2.S.1.1 Nomenclature of immunogenic substance

The following information should be provided:

a) Name of the immunogenic substance based on the WHO or pharmacopoeial requirements, as appropriate:

b) The biological name (including strain and/or clone designation) or chemical name, including any approved name:

c) For combination vaccines, each immunogenic substance, which will be pooled, combined with other antigens and formulated:

d) Any chemical modification or conjugation of the immunogenic substance

e) List of any inactive substances, which may be present in the immunogenic substance including impurities and residual proteins.

3.2.S.1.2 Structure

Provide the 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.

3.2.S.1.3 Physicochemical Characterization and Biological Activity

3.2.S.1.3.1 Physicochemical Characterization

Provide the description and characterization of the immunogenic substance, including physicochemical properties. The information provided should include the degree of derivatization or conjugation, the amount of unmodified substance removal of free materials (e.g., toxins, linkers, etc.), and the stability of the modified substance

Additional physicochemical characterization may be required for modified immunogenic substances such as conjugates, multiple antigen peptides (MAP), impurities, residual proteins and residual rDNA or those undergoing further chemical or enzymatic modifications.

3.2.S.1.3.2 Biological Activity

A description and results of all relevant in vivo and in vitro biological testing (bioassays) performed on the manufacturer's reference standard lot or other relevant lots to demonstrate the potency and activity (ies) of the immunogenic should be provided.

This section should include a complete description of the protocol used for each bioassay, the control standards used, the validation of the inherent variability of the test, and the established acceptance limits for each assay. The characteristics of specific antibodies used in the immunochemical or serological assays should also be included.

Further information can be obtained from ICH guideline Q6B.

3.2.S.1.4 General description of the starting materials of biological origin used to obtain or extract the immunogenic substance

For each biological starting material a summary of safety of the material with respect to contamination by other microorganism should be provided:

a) Strain(s) information should be provided on the origin, number of passes, identification, analysis certificates, processes of attenuation, development or construction and genetic stability, depending on type of vaccine strains.

b) 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, information should be provided to demonstrate that the characteristics of the cells remain unaltered in the passes used in production and successively. The cell bank system generally consists of two tiers: a Master Cell Bank (MCB), and a Working Cell Bank (WCB) generated from the MCB for vaccine manufacturing. In some instances, another tier of 'Primary Cell Bank' may be established which allows the manufacturers to perform extensive testing on a pool of cryopreserved primary cells prior to their usage in vaccine production.

(i) Master Cell Bank (MCB): The cells comprising the MCB should be identified and a complete history and characterization of the MCB should be provided. For recombinant products, the cell substrate used to establish the MCB is the transfected cell containing the desired genetic construct, which has been cloned from a single cell progenitor. For non-recombinant products, the cell substrate is the cell from the parental cell line chosen for preparation of the MCB without further

modification. For a diploid cell line the population doubling level chosen for the MCB should be given.

(ii) Working Cell Bank (WCB): This section should contain a description of the procedures used to derive a WCB from the MCB. The description should include the identification system used for the WCB as well as the procedures for storage and cataloguing of the WCB. The assays used for qualification and characterization of each new WCB should be included with the results of those assays for the WCB currently in use. If applicable, a description of animal passage of the WCB performed to assure the presence of virulence factors, which are protective antigens, should be supplied. This section should also contain a description of the methods and procedures used to assure culture purity and identity.

(iii) End of Production Cells (EPC): For rDNA derived immunogenic substances, a detailed description of the characterization of the EPC that demonstrates that the biological production system is consistent during growth should be provided. The results of the analysis of the EPC for phenotypic or genotypic markers to confirm identity and purity should be included. This section should also contain the results of testing supporting the freedom of the EPC from contamination by adventitious agents. The results of restriction enzyme analysis of the gene constructs in the EPC should be submitted. For recombinant DNA (rDNA) derived products and rDNA modified cell substrates, detailed information shall be provided regarding the host cell and the source and function of the component parts of the recombinant gene construct.

(iv) Use of fertilized eggs; Information on their origin, identification, quality certificates should be provided.

Further information can be obtained in ICH guidelines Q5A, Q5B, Q5C and Q5D

3.2.S.1.5 General Description of the raw materials

These are raw materials used in the preparation process from which the immunogenic substance is not directly derived, such as culture media, bovine fetal serum, etc. Applicant should submit information on manufacturer(s) (name and address), quality certificates and any 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 and the risk of porcine circoviruses.

A list of all materials (culture media, buffers, resins for peptide synthesis, chemicals, columns, etc.) used in the manufacture of the immunogenic substance, and their tests and specifications, or reference to official compendia, should be provided.

For purchased materials, representative certificates of analysis from the supplier(s) and/or manufacturer's acceptance criteria should be provided.

3.2.S.2 Manufacture of the Immunogenic Substance

3.2.S.2.1 Manufacturer(s)

Provide the name(s), physical address(es) of the manufacturing site, unit(s) and/or block(s) involved in all stages of manufacturing processes. Provide a valid manufacturing licence and/or certificates of GMP compliance of the sites and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the immunogenic substance. This may include independent contractors or other company subsidiaries serving as contractors, or other locations/sites owned and operated by the applicant. Also in this section there should include a discussion of the operations performed by each party and the responsibilities delegated to each party by the applicant.

Manufacture of Other substances**:** Provide a comprehensive list of all additional products that are manufactured or manipulated in the same areas used to produce the immunogenic substance that is the subject of this application should be provided.

3.2.S.2.2 Immunogenic substance manufacturing process

Provide detailed description of the manufacturing processes and controls to demonstrate proper quality control and prevention of possible contamination with adventitious agents. The inclusion of a list of all relevant SOPs is required; however, actual copies of the SOPs are not required, as these will be verified on site during GMP inspection.

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 passages.

The description should be accompanied with a flow chart of the production process, showing all the manufacturing steps, including intermediate processes. For multiple immunogenic substances prepared from a single strain, a common flow chart is acceptable, through the propagation and harvest cycle, with indications of where the processing diverges. This flow chart should show the steps in production, equipment and materials used, room or area where the operation is performed (may reference diagrams in other sections of the application), and a complete list of the in process controls and tests performed including specifications and acceptance criteria on the product at each step.

In-process holding steps should be included, with time and temperature limits indicated. For chemical synthesis, a flow chart should include all the steps in a general synthesis cycle with other specific steps, such as fragment condensation or peptide cleavage, indicated.

For recombinant DNA (rDNA) derived products and rDNA-modified cell substrates, detailed information should be provided regarding the host cells, and the source and function of the component parts of the recombinant gene construct.

For synthetic immunogenic substance such as linear or complex synthetic peptides, or modified synthetic or semi-synthetic immunogens like lipopeptides, peptide to carrier protein or polysaccharide to carrier protein conjugates, the detail of the peptide synthesis including purification procedures should be provided.

Provide a description of the lot identification system i.e. 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.

Provide a description and validation of the inactivation or detoxification process. The methods and agents used, parameters controlled, and production stage in which it is performed should be described where applicable. For toxoid/inactivated vaccine, the detoxification/inactivation procedures should be described in detail for the immunogenic substances:

a) The method(s) and agent(s) used for detoxification/inactivation;
b) The stage in production where detoxification/inactivation is performed; and
c) The parameters that are monitored.
d) Verification of the adequacy of the method for detoxification/inactivation should be provided.

Description of the purification process: Method used reagents, and materials used, operating parameters controlled, and specifications. The conditions for the use and re-use of membranes and chromatography columns and the respective validation studies should be described.

Description of the conjugation process: Indicate when applicable and/or when a modification of active ingredients is done. 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 immunogenic substance: Description of the steps performed to stabilize the immunogenic substance, 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. This section should include detailed information on any reprocessing that may be done on each immunogenic substance. The information provided for each reprocessing procedure should include:

a) A description of the conditions or criteria, determined from process controls or specifications, which indicate the need for re-processing; a description of the reprocessing step;

b) A description of any additional or modified in-process controls or specifications which are included to monitor re-processing steps;

c) A description of the modifications in batch numbers and documentation of re-processing in the Batch Production Record (BPR); and

d) The evidence derived from validation studies, which assure that product identity, purity, potency, and stability is preserved for re-processed batches.

e) Methods and agents used, parameters controlled, and production stage in which it is performed.

Filling Procedure: Provide 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.

3.2.S.2.3 Controls of critical steps and intermediates

Identification of critical steps in the process and controls performed, from the original inoculation until the active substance is obtained, defining the operational parameters or aspects to be controlled during the critical stages, including specifications should be provided.

For all in-process testing indicated in the flow charts, a brief description of the sampling procedures and the test methods used should be provided. For testing performed at significant phases of production criteria for accepting or rejecting an in-process batch should be specified.

3.2.S.2.4 Process Validation and/or evaluation

Provide information on validation/and or evaluation of the manufacturing process of immunogenic substance. It should include reprocessing, sterilization, establishment of critical steps, and criteria for establishing the control limits on the critical steps. A summary report, including protocols and results, should be provided for the validation studies of each critical process or factor that affects immunogenic substance specifications, i.e., a decision to accept or reject a batch.

Consistency of the manufacturing process for each vaccine component shall be demonstrated by manufacturing at least three, preferably consecutive batches of immunogenic substances of a size corresponding to that of routine production.

Further requirements on individual vaccines can be obtained in Guidelines for Validation of Production Processes for Vaccines for WHO Prequalification-Compliance Expectations

3.2.S.3 Characterization of the immunogenic substance

This section should contain a description of all analytical testing performed to characterize the immunogenic substance with respect to identity, purity, potency, and stability.

Test results should include actual data such as tabular data, legible copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis, or other appropriate formats. Results for quantitative assays should be presented as actual data, not generally as "Pass" or "Fail."

Impurities that should be characterized and quantitated include:

a) Product related impurities (variants or alterations of antigen occurring during processing or storage).

b) Process related impurities: Media components; Cell substrate proteins or nucleic acids; or Process reagents which have not been removed by the purification process.

Note: For highly purified substances, purity in reference to the theoretical composition should be presented.

Further requirements on individual vaccines can be obtained from guideline on Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks and ICH guideline Q6B.

3.2.S.4 Quality control of the immunogenic substance

3.2.S.4.1 Specification of the immunogenic substance

This section should contain the specifications and tests for each immunogenic substance.

The specifications should include assays for identity, purity, potency (biologic effect), physicochemical measurements, which predict potency, and measures of stability.
In some cases, test results for the stabilized intermediates of component antigens should be included in the final release of the immunogenic product.

Information on test procedures and acceptance criteria can be obtained in ICH guideline Q6B.

3.2.S.4.2 Description of the analytical procedures

Provide full description of analytical procedures used for carrying out tests provided in the specification where such methods are adopted from a standard, a declaration should be given and any differences should be described.

Further requirements can be obtained in ICH guideline Q6B.

3.2.S.4.3 Analytical Method validation

All analytical methods used in carrying out assay and impurities of immunogenic substances should be validated and validation reports should be provided.

The results of validation studies demonstarting the specificity, sensitivity, and variability of each method used for release testing shall be provided. Where applicable this shall include descriptions of reference standards and their qualification. For Analytical methods in compendial sources, the appropriate citations should be provided.

Further requirements can be obtained in WHO Recommendation for the preparation, characterization and establishment of international and other biological reference standards

3.2.S.4.4 Batch analysis and Production consistency

Provide a summary protocol of the production and control of three consecutive lots of immunogenic substances, analysis certificates in the event this information is not included in the summarized protocol for the finished immunogenic substances, and an analysis of the results of these lots in terms of production consistency.

6.2.S.4.5 Justification of the quality specifications

Discussion of the impurities in the immunogenic substance should be provided. The identity and quantity of impurities should be provided along with the analytical data (gels, elution profiles, Western blots, etc.), which support the impurities profile.

Provide a justification for all the tests and acceptance criteria. Further requirements can be obtained in ICH guideline Q6B.

3.2.S.5 Reference standards or materials

Provide a detailed description of the reference standards or materials used and their certificate of analysis. A description of the preparation, characterization, and stability of primary and working reference standards should be provided. A detailed description of the procedures to qualify new lots of reference standards and acceptance criteria for a new reference standard should be included. The rationale and use of the reference standards in assuring consistency in product characteristics shall be described.

3.2.S.6 Packaging and container closure system

Provide the full description of the container closure system in which the immunogenic substance will be stored until used for preparing the finished immunogenic 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.S.7 Stability

Provide information on the stability of the immunogenic substance and any in-process material at each holding step, as outlined in the guideline references below.

a) 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.

b) 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.

c) Stability data should include complete data from each batch evaluated during stability studies.

d) Storage and transportation conditions for the immunogenic substance, when applicable. Describe the equipment used, areas, and buildings (if pertinent) and the shipping and storage conditions.

Further information can be obtained in Guidelines on Stability Evaluation of Vaccines ICH Guideline Q5C.

3.2.P Finished Immunogenic Product

This section should contain information on the final immunogenic product including all immunogenic substances, adjuvants and excipients in the final immunogenic product. If any proprietary preparations or mixtures are used as components, the information provided should include a complete statement of composition and other information that will properly describe and identify these materials.

Appropriate information may be cross-referenced to those under immunogenic substance section.

For diluents and reconstitution solvents, entire section 3.2.P should be included in the submission.

3.2.P.1 Description and Composition

Provide a description of the finished immunogenic product, its composition, a list all components in the finished immunogenic product, including immunogenic substance(s), adjuvants, preservatives, stabilizers, and excipients, stating the function of each of them and other ingredients, with their unit doses and batch quantities specified.

Where applicable, the quantity may be expressed as percentage or molarity.

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

Tables in Quality Overall Summary should be used to summarize unit composition of the immunogenic product

3.2.P.2 Formulation development

3.2.P.2.1 Formulation development

Provide the studies performed to establish the dosage form, formulation, manufacturing process, and the container closure system used for final immunogenic product. The studies to be described in this section are different from the routine quality control tests performed in accordance with the product specifications.

Further information can be obtained in ICH guideline Q8.

3.2.P.2.2 Immunogenic Substance

Compatibility information/data with the rest of the components in the finished immunogenic product, including adjuvant, preservative, and stabilizers should be demonstrated, as applicable. Compatibility with diluents or reconstitution solvent should also be provided. For products that contain more than one immunogenic substance, the compatibility of the immunogenic substances with each other should also be evaluated.

3.2.P.2.3 Adjuvant, preservative, stabilizers, and excipients

This section should contain a list of the chemical formula and precise quantity of each adjuvant per unit dose. Whether the quantity of adjuvant is determined by assay or by calculation should be indicated and the method used should be described.

Adjuvant

The mechanism of association and association efficiency between antigen and adjuvant should be defined and described. Aspects that are critical for the biological properties of the adjuvant-antigen combination (e.g. adsorption, binding characteristics) should be identified and monitored. If more than one adjuvant is to be incorporated, appropriate information for each adjuvant should be supplied and compatibility studies should be performed on the intended combination of adjuvant(s) and antigen(s).
The entire manufacturing process of the adjuvant-antigen combination should be described in detail.

Preservatives

Each preservative should be identified by chemical as well as any trade name or reference to compendial sources. A rationale should be provided for the inclusion of a preservative in single dose finished products. The results of the preservative effectiveness studies should be included or reference may be made to other files.

Further requirements for DT based combined vaccines can be obtained from the WHO guideline on “recommendations to assure the quality, safety and efficacy of DT-based combined vaccines”

Stabilizers and Excipients

This section should contain a list of all inactive components with the rationale for the inclusion of each in the final product. The information provided should include certificates of analysis, results of analytical testing, or other information that will describe or identify each excipient. If compendial excipients are used, citations may be included *in lieu* of analytical testing. Excipients may include, but not be limited to:

a) Diluents (molarity, pH should be included for these);

b) Bulking agents;

c) Adsorbents (other than adjuvants); and

d) Stabilizers (e.g., sugars, wetting agents).

3.2.P.2.4 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

3.2.P.2.5 Physicochemical and Biological Properties (name, dosage form)

Parameters relevant to the performance of the drug product, such as pH, biological activity or potency, and/or immunological activity, should be addressed.

3.2.P.2.6 Development of the manufacturing process

Provide description of the selection and optimization of the manufacturing process, particularly for critical aspects. The scientific rationale for the selection, optimization and scale-up of the manufacturing process should be explained, in particular the critical aspects.

3.2.P.2.7 Container closure system

The suitability of the container-closure system used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the finished product)

3.2.P.2.8 Microbiological Attributes (name, dosage form)

Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases) and/or microbial species should be evaluated. The selection and effectiveness of preservative systems in products containing antimicrobial preservatives should be discussed.

Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product. For the special case of adventitious viral or mycoplasma contamination, the concept of action limits is not applicable, and the strategies proposed in ICH guidelines; Q5A and Q5D.

3.2.P.2.9 Compatibility (name, dosage form)

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g. precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

3.2.P.3 Manufacture of finished immunogenic product

3.2.P.3.1 Manufacturer

Provide the name(s), physical address(es) of the manufacturing site, unit(s) and/or block(s) involved in all stages of manufacturing processes. Applicant should provide valid manufacturing licence and/or certificates of GMP compliance of the sites and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the finished immunogenic products.

3.2.P.3.2 Batch formula

Provide the formula of the production lot, including a list of all components of the immunogenic product to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

3.2.P.3.3 Description of the manufacturing process

Provide 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, equipment and materials used, the room or area where the operation is performed (may reference the simple floor diagram), in process controls, and the critical points identified. Further requirements for DT based combined vaccines can be obtained in WHO guideline “recommendations to assure the quality, safety and efficacy of DT-based combined vaccines”

3.2.P.3.4 Control of critical and intermediate steps

Provide the tests and acceptance criteria developed to identify the critical steps in the manufacturing process and how they were controlled. A listing of the in-process controls and tests performed on the product at each step should be submitted. Information on the quality and control of intermediates isolated during the process should be provided.

3.2.P.3.5 Validation and/or evaluation of the processes

Provide a 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. Further requirements can be obtained in Validation of Production Processes for Vaccines for WHO Prequalification- Compliance Expectations documentation.

3.2.P.3.6 Description of the batch identification system

Provide information on how the lots are defined in the stage of filling, lyophilisation (if it applies) and packaging.

3.2.P.4 Control of the adjuvant, preservative, stabilizers, and excipients

3.2.P.4.1 Specifications

Provide information on the specifications for all the substances (adjuvant, preservative, stabilizers, and excipients etc.) employed in the formulation of the finished immunogenic product that are different from the immunogenic substance. List of raw materials meeting in-house specifications including the tests performed and specifications of Biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephalopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product including Certificate of Suitability (CEP). The information should be provided as appendices to module 3. Further information can be found in ICH guideline Q6B

3.2.P.4.2 Analytical procedures

Provide the description or bibliographic reference of the analytical methods used to control all the substances (adjuvant, preservative, stabilizers, and excipients etc.) employed in the formulation of the finished immunogenic product.

3.2.P.4.3 Validation of the analytical procedures

All analytical method used to control the substances (adjuvant, preservative, stabilizers, and excipients etc.) used in formulating the final product should be validated and validation reports should be provided if applicable.

Further information can be found in ICH guidelines Q6B and Q2B

3.2.P.4.4 Justification of specifications

Provide a justification of the specifications of the substances (adjuvant, preservative, stabilizers, and excipients etc.) used in formulating the final product. Further information can be found in ICH guideline Q6B

3.2.P.4.5 Substances of Human or Animal Origin

Provide information on the source, origin, description of the quality tests performed, specifications, determination of adventitious agents, and viral safety. For all ingredients of human or animal origin, testing results or certificates of analysis demonstrating their freedom from adventitious agents should be provided.

3.2.P.4.6 Novel 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.

Further information can be obtained from EMA guidelines on adjuvants for vaccine for human use, WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccine, Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines and WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products.

3.2.P.5 Control of the finished immunogenic product

3.2.P.5.1 Specifications

This section should contain a description of tests and specifications for finished immunogenic product. At minimum, specifications should contain test and acceptance criteria for description and appearance, identity, quantity, potency, purity and impurities.

Further information on requirements for tests for sterility, Bacterial endotoxins, pyrogenicity etc. can be obtained in individual vaccines WHO TRS.

General information on specifications can be found in ICH guideline Q6B.

3.2.P.5.2 Analytical procedures

Provide information on the analytical procedures used for quality control of the finished product should be provided.

3.2.P.5.3 Validation of the analytical procedures

Provide information on the validation of the analytical procedures for the finished immunogenic product, including experimental data. This information should include complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.

Further information can be found in ICH guidelines Q6B and Q2B.

3.2.P.5.4 Lot consistency and analysis

Provide a description of all test methods selected to assure the identity, purity, strength and/or potency, as well as the lot-to-lot consistency of the finished immunogenic product and the specifications used for the immunogenic product.
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. Batch/lot release certificates issued by the relevant regulatory Authority in the country of the manufacture with the aim of the confirmation of consistency of production at each lot of vaccines should be submitted for three consecutive batches.

3.2.P.5.5 Characterization and/or determination of impurities

Provide details on the characterization and/or determination of impurities, as applicable, depending on the method used to manufacture the immunogenic product submitted for market authorization.

3.2.P.5.6 Justification of specifications

Provide justification of the specifications proposed for the immunogenic product. Further information can be found in ICH guideline Q6B.

3.2.P.5.7 Analytical certificates

Provide certificates of analysis and analytical results for at least three consecutive batches of the immunogenic product signed by manufacturer.

Further requirements can be obtained in the ICH guideline Q6B and the WHO Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities

3.2.P.6 Reference standards and materials

Provide information on the reference standards and/or materials used in the tests to control the finished immunogenic product. Reference should be made to ICH guideline Q6B for further guidance.

3.2.P.7 Container Closure System of the Finished Immunogenic Product

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate).

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. Suitability information should be located in 6.2.P.2.

Further requirements can be obtained in the WHO Guidelines on packaging for pharmaceutical products

3.2.P.8 Stability of the Finished Immunogenic Product

3.2.P.8.1 Protocols and results of the stability study that justify the proposed validity period

Submit the stability study 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 immunogenic product prepared from different lots of immunogenic substances, conclusions, and proposed validity period. The professional in charge of the study should sign the stability studies. 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.

3.2.P.8.2 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.

3.2.P.8.3 Stability data

Evidence shall be provided to demonstrate that the product is stable for the proposed validity period under the indicated storage conditions.
The stability of each dosage form should be separately documented.
The summary results, which support the proposed expiration-dating period, under recommended conditions, in the final container and closure system, should be provided.

Stability data submitted should be for at least three consecutive batches. Information on stability of final immunogenic product, quality control methods and rationale for the choice of tests for determining stability should be provided.

Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production.

Describe the policy for assigning the date of manufacture of each component as well as the final product (e.g. combination vaccine) and diluents, as appropriate.

In addition to final product stability data at the recommended storage temperature, the stability data at elevated temperatures should be sufficient to justify the choice of Vaccine Vial Monitor (VVM) for use with the product.

For lyophilized products the data supporting the shelf-life of the product following reconstitution should be included.

If the immunogenic product is frozen, data supporting the stability of the product through a stated number of freeze-thaw cycles should be provided.

A plan for an on-going stability program should be provided. This should include the protocol to be used, number of final lots to be entered into the stability protocol each year and how such lots will be selected. A stability study protocol should be provided.

For multi-dose vaccines, reference should be made to the WHO policy statement Multi-dose Vial Policy (MDVP) for vaccines.

For extended controlled temperature conditions (ECTC) stability, reference should be made to the WHO Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions

3.2.P.8.4 Description of the procedures used to guarantee the cold chain as per WHO guidelines on the international packaging and shipping of vaccines

Describe in detail the measures used to guarantee adequate temperature and humidity conditions for shipping the finished immunogenic 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. Signed declaration from authorized personnel should be provided.

Further requirements can be obtained in the WHO Guidelines on stability evaluation of vaccines, 2006 and ICH guideline Q5C.

3.2.A Appendices

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

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g. cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

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

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents: Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

For further guidance refer to the WHO Recommendations for the evaluation of animal cell cultures as substrates for manufacture of biological medicinal products and for characterization of cell banks

For viral adventitious agents: Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable.

For further guidance refer ICH guidelines Q5A, Q5D, and Q6B.

Materials of biological origin: Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided.

Testing at appropriate stages of oroduction: The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an

appropriate stage of manufacture, that the product is free from viral contamination should be provided.

Viral Testing of Unprocessed Bulk: In accordance with ICH guidelines Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies: In accordance with ICH guideline Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5)

For further guidance refer to ICH guidelines Q5A, Q5D, and Q6B.

3.2.A.3 Excipients

3.2.R: Summary Lot Protocols

Summary lot protocols should be provided. This should be in accordance with the WHO Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities

3.3 Literature References

Key literature referenced should be provided, if applicable.

4.0 MODULE 4: NON-CLINICAL INFORMATION

Pre-clinical testing is a prerequisite to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product characterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans.

Non-clinical studies should comply with the WHO Guidelines on Non-Clinical Evaluation of Vaccines

The submission in this section should be organised as summarised below:

4.1 Table of contents of module 4

4.2 Reports on studies

4.2.1 Pharmacology

4.2.2 Pharmacodynamic studies (immunogenicity of the vaccine)

4.2.3 Pharmacodynamic studies of adjuvants (if applicable)

4.2.4 Pharmacokinetics

Pharmacokinetic studies, when applicable depending on the type of vaccine or when new substances for example so called "Novel" adjuvants are used in the formulation of the product, new routes of administration, or pharmaceutical forms that require the respective pharmacokinetic evaluation.

4.2.5 Toxicology

a) General toxicology

Information should be presented on:

i. Design of the study and justification of the animal model
ii. Animal species used, age, group size
iii. Dose, route of administration, and control groups
iv. Parameters monitored
v. Local tolerance

b) Special toxicology for vaccines (when applicable)

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

4.2.6 Special considerations

a) Live attenuated vaccines

An evaluation should be presented of the possibility of microorganism shedding through natural avenues of excretion.

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

For further guidance, refer to WHO guidelines on nonclinical evaluation of vaccines and WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines.

4.3 Literature references

Include literature references if used.

5.0 MODULE 5: CLINICAL STUDIES

This section details particulars of tests, which have been performed in humans regarding the safety and efficacy of the vaccine. Clinical studies shall be designed and conducted to meet WHO and ICH GCP principles.

Tabulated summary: The applicant shall provide tabulated summary of the clinical development program of the vaccine, including any critical parameters that may have changed during the clinical development.

Clinical summary: Provide detailed summary and interpretation of the safety, efficacy and immunogenicity data obtained from clinical studies that supports the current prescribing information.

Clinical Expert Report: Applicant shall provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided)

The clinical studies should follow the WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations. Further important information can be found in the EMA Guideline on Clinical Evaluation of New Vaccines.

5.1 Table of contents of Module 5

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 immune competent healthy adults (50-200) who usually present low risk of being infected by the disease the vaccine is intended for.

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 of subjects (200-600) and are usually controlled and randomized. The main objectives of these studies are to demonstrate the immunogenicity of the active(immunogenic) component(s) and safety in the target population 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).

The populations should be less restricted and should contain less exclusion criteria than studies in Phase II, so that the results of Phase III studies can better extrapolated to the general population. Different ethnic subpopulations including African natives and different age groups depending on the kind of preventable disease should be included.

Several thousand subjects can be enrolled in these studies (the number will be defined by the end point of the study). Serological data is 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.

Depending on the nature of the disease pre-immunization antibody titers may be very important for sufficient evaluation of the efficacy and safety of the vaccine and should be fully evaluated (for example Dengue fever). In case of high pre-immunization antibody titers results after vaccination may not be transferable to a naïve population. At minimum 3000 participants should be evaluated for safety reasons. Depending on the disease, placebo or an active comparator design can be appropriate. Efficacy analysis should always be submitted including the pre-protocol and the (intention-to-treat) ITT analysis.

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.

In special situations with well-known complications of precursor vaccines, the new product must be evaluated in well-designed safety studies with adequate endpoints (for example rotavirus vaccines and intussusception). In general, and especially if so called “novel adjuvants” are used, careful evaluation of new onset of autoimmune diseases (NOAD) and new onset of chronic diseases (NOCD) is mandatory.

5.2.5 Adjuvants

Evidence and scientific support that justifies the use of adjuvants, when applicable. The use of a so called “novel adjuvant” should be justified by superior efficacy compared to non-adjuvant or conventionally adjuvant products (for example aluminum salts). The potential risk of the so called “novel adjuvant” on the incidence of new onset of autoimmune diseases (NOAD) and new onset of chronic diseases (NOCD) must be fully evaluated.

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 follow-on 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.

6.0 POST MARKET SURVEILLANCE FOR VACCINES

In this section, applicant should provide the following post approval commitments:

a) An outline of the post marketing pharmacovigilance plan for the vaccine.

b) Periodic benefit-risk evaluation report in accordance with ICH Guideline E2C(R2) Clinical Safety Data Management: Periodic benefit risk evaluation report

c) In the case of vaccines that have recently been registered/ licensed, applicant should provide information on any on-going phase IV studies or on any active monitoring of the safety profile that is taking place including adverse events following immunization (AEFI).

d) Risk management plan.

Further requirements can be obtained from the WHO Expert Committee on Biological Standardization guideline, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products and ICH guideline E2E.

7.0 REFERENCES

EMEA Guideline on Adjuvants in Vaccines For Human Use
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EMEA Guideline on Clinical Evaluation of New Vaccines
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-new-vaccines_en.pdf

Guidance for Industry For The Evaluation Of Combination Vaccines For Preventable Diseases: Production, Testing and Clinical Studies
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evaluation-combination-vaccines-preventable-diseases-production-testing-and

Guidelines for good clinical practice (GCP) for trials on pharmaceutical products WHO TRS 850 Annex 3
http://apps.who.int/medicinedocs/pdf/whozip13e/whozip13e.pdf

Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities
https://www.who.int/biologicals/Guidelines_for_Lot_Release_AFTER_ECBS_27.1.2011.pdf?ua=1

Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations WHO TRS 1004 Annex 9
http://apps.who.int/medicinedocs/documents/s23328en/s23328en.pdf

Guidelines on packaging for pharmaceutical products WHO TRS 902 Annex 2
http://apps.who.int/medicinedocs/documents/s19638en/s19638en.pdf

Guidelines on Stability Evaluation of Vaccines
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Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated) TRS 932 Annex 2
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http://apps.who.int/medicinedocs/documents/s22428en/s22428en.pdf

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ICH Harmonised Tripartite Guideline Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products Q5C
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http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

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ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
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ICH Topic Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-d-derivation-characterisation-cell-substrates-used-production-biotechnological/biological-products-step-5_en.pdf

ICH Topic Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf

Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks TRS 978 Annex 3
https://www.who.int/biologicals/Cell_Substrates_clean_version_18_April.pdf

Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines WHO TRS 980 Annex 6
https://www.who.int/biologicals/vaccines/Combined_Vaccines_TRS_980_Annex_6.pdf?ua=1

Validation of Production Processes for Vaccines for WHO Prequalification Compliance Expectations
https://www.who.int/immunization_standards/vaccine_quality/validation_guide_july2013.pdf?ua=1

WHO Expert Committee on Biological Standardization WHO TRS 924
http://apps.who.int/medicinedocs/documents/s16104e/s16104e.pdf

WHO glossary of terms
https://www.who.int/hia/about/glos/en/

WHO guidelines on nonclinical evaluation of vaccines WHO TRS 927 Annex 1
https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products
https://apps.who.int/iris/bitstream/handle/10665/68932/a85721.pdf?sequence=1&isAllowed=y

WHO Model inserts
http://www.who.int/immunization_standards/vaccine_quality/model_inserts/en/

WHO Policy Statement: Multi-dose Vial Policy (MDVP)
https://apps.who.int/iris/bitstream/handle/10665/135972/WHO_IVB_14.07_eng.pdf?sequence=1

APPENDIX I: APPLICATION FORM FOR REGISTRATION OF HUMAN VACCINES

National Drug Authority
Plot No. 19 Rumee Towers, Lumumba Avenue,
P.O. Box 23096, Kampala, Uganda.
email: ndaug@nda.or.ug; website:
www.nda.or.ug
Tel: +256-414-255665, +256-414-347391/2

Doc. No.: PAR/FOM/335
Revision No.: 0
Effective Date: 14 Oct 2019

MODULE 1: ADMINISTRATIVE INFORMATION	
1.0 PARTICULARS OF THE FINISHED PRODUCT	
1.1	Type of the medicinal product application New (Innovator) Generic(Traditional/Follow on vaccines) Renewal
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the immunogenic substance
1.4	Strength of immunogenic substance(s) per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: E-Mail:	
1.6	Dosage form and route of administration
1.6.1	Dosage form:
1.6.2	Route(s) of administration (
1.7	Packing/pack size:
1.8	Visual description (Add as many rows as necessary)

1.9	Proposed shelf life (in months):
1.9.1	Proposed shelf life (after reconstitution or dilution) (if applicable):
1.9.2	Proposed shelf life (after first opening container):
1.9.3	Proposed storage conditions:
1.9.4	Proposed storage conditions after first opening:
1.10	Other related Vaccine products registered or applied for registration
1.10.1	Do you hold Marketing Authorization (s) of other Vaccines (s) containing the same active Immunogenic (s) in Uganda? If yes state; ▪ Product name (s), strength (s), dosage form (s): ▪ Marketing authorization number(s): ▪ Indication(s):
1.11	Pharmacotherapeutic group and ATC Code
1.11.1	Pharmacotherapeutic group:
1.11.2	ATC Code: (Please use current ATC code)
1.11.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.12	Distribution category: ☐ POM (Prescription only Medicine) unless otherwise,provide justification)
1.13	Country of origin:
1.14	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons

☐Authorised Country: Date of authorisation (dd-mm-yyyy): Proprietary name: Authorisation number:	☐ Withdrawn (by applicant after authorisation) Country: Date of withdrawal (dd-mm-yyyy): Proprietary

☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal: SDRA-Documents to be attached:	name: Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name: SDRA-Documents to be attached:
1.15	List SRAs where the vaccine is approved. SDRA-Documents to be attached:
1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	Name(s) and physical address (es) of the manufacturing site of the finished product, including the final product release if different from the manufacturer. Alternative sites should be also declared here. All manufacturing sites involved in the manufacturing

	process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary
Name: Company name: Address: Country: Telephone: E-Mail:	
1.16.2	Name(s) and physical address(es) of the manufacturer(s) of the active immunogenic substance (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active immunogenic substance, including quality control / in-process testing sites should be listed.
Name: Company name: Address: Country: Telephone: E-Mail:	
1.17	Name and address (physical and postal) of the Local Technical Representative (if applicable)
Name:	

Company name: Address: Country: Telephone: E-Mail:	
1.18	Name and address (physical and postal) of the person or company responsible for pharmacovigelance
Name: Company name: Address: Country: Telephone: E-Mail:	
1.19	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Finished Product.
1.20	Qualitative and Quantitative composition of the immunogenic substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. per ml).

Name of immunogen(s)	Quantity / dosage unit	Unit of measure	Reference/ monograph standard
1.			
2.			
3.			
e.t.c			
Name Excipient(s)			
1.			
2.			

3				
e.t.c				
Note: Only one name for each substance should be given in the following order of priority: INN, Pharmacopoeia, common name, scientific name.				

1.21	Name and address (physical and postal) of the Clinical Research Organisation(s) where the clinical studies of the product were conducted.
Name: Company name: Address: Country: Telephone: E-Mail:	
1.22 DECLARATION BY AN APPLICANT I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge. I further confirm that the information referred to in my application dossier is available for verification during GMP inspection.	

	I also agree that I shall carry out pharmacovigelance to monitor the safety of the product in the market and provide safety update reports to the National Drug Authority of Uganda. I further agree that NDA can contact and share submitted confident content from the applicant and evaluation reports with Stringent Drug Regulatory Authorities (SDRAs) for scientific discussion and advice. It is hereby confirmed that fees will be paid/have been paid to NDA * Name: ……..…… …… Position in the company:…… Signature: …… Date:…….. Official stamp:…….. * Note: If fees have been paid, attach proof of payment

APPENDIX II: EXPERT DECLARATION FORM

National Drug Authority
Plot No. 19 Rumee Towers, Lumumba Avenue,
P.O. Box 23096, Kampala, Uganda.
email: ndaug@nda.or.ug; website: www.nda.or.ug
Tel: +256-414-255665, +256-414-347391/2

Doc. No.: PAR/FOM/336
Revision No.: 0
Effective Date: 14 Oct 2019

The following is an example of a suitable declaration form:

Quality /Non-clinical / Clinical (delete those not appropriate)
I, the undersigned, declare that I have:

i. The suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed curriculum vitae).

ii. Fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.

iii. Provided a report based on my independent assessment of the data provided.

iv. Based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

I further declare that this expert report represents my own view.
Further, I declare the following to be the full extent of the professional relationship between the applicant and myself:

.....

.....

APPENDIX III: QUALITY OVERALL SUMMARY

National Drug Authority
Plot No. 19 Rumee Towers, Lumumba Avenue,
P.O. Box 23096, Kampala, Uganda.
email: ndaug@nda.or.ug; website: www.nda.or.ug
Tel: +256-414-255665, +256-414-347391/2

Doc. No.: PAR/FOM/337
Revision No.: 0
Effective Date: 14 Oct 2019

2.3.S Immunogenic substance (name, manufacturer)

2.3.S.1 General information, starting materials and raw materials

2.3. S.1.1 Nomenclature
(a) WHO or Pharmacopoeal name(s)
(b) Biological name
(c) For combination vaccines (names of immunogenic substances)
(d) Chemical modification/conjugation of the immunogenic substance

2.3. S.1.2 Structure
(a) Structural formula
(b) Schematic amino acids sequence/molecular formula
(c) Relative molecular mass

2.3.S.1.3 Physicochemical Characterization and Biological Activity
2.2.S.1.3.1 Physicochemical Characterization
2.2.S.1.3.2 Biological Activity
2.3.S.1.4 General description of the starting materials of biological origin used to obtain or extract the immunogenic substance
2.3.S.1.5 General description of the raw materials
2.3.S.1.6 Analytical certificates signed by the manufacturer and the applicant

2.3.S.2 Manufacture of the immunogenic substance (name, Manufacturer)

2.3.S.2.1 Manufacturer(s)

(a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, and storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

Name and address (including block(s)/unit(s))	Responsibility

(b) Manufacturing authorization for the production of API(s) and, where available, certificate of GMP compliance (GMP information should be provided in *Module 1*):

2.3.S.2.2 Immunogenic substance manufacturing process

(a) Flow diagram of manufacturing process
(b) Narrative description of the manufacturing process (es)
(c) In process holding steps
(d) Description of lot identification system
(e) Description and validation of the inactivation or detoxification process
(f) Description of the purification process
(g) Description of the conjugation process
(h) Stabilization of the immunogenic substance
(i) Reprocessing (if applicable)
(j) Filling Procedure

2.3.S.2.3 Control of critical steps and intermediates

(a) Critical steps in the process and controls performed
(b) Description of sampling procedures

2.3.S.2.4 Process Validation and/or evaluation

2.3.S.3 Characterization of the immunogenic substance

(a) Details of analytical testing
(b) Impurities
    (i) Product related Impurities
    (ii) Process related Impurities

2.3.S.4 Control of the Immunogenic Substance

2.3.S.4.1 Specifications

2.3.S.4.2 Description of Analytical Procedures

2.3.S.4.3 Analytical Method validation

2.3.S.4.4 Batch analysis and Production consistency

2.3.S.4.5 Justification of the quality specifications

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

(a) Source (including lot number) of primary reference standards or reference materials (e.g.Ph.Int., Ph.Eur., BP, USP, in-house)
(b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis)
(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard)

2.3.S.6 Packaging and container closure system of the immunogenic substance

2.3.S.7 Stability of the immunogenic substance

(a) Stability Studies Protocol
(b) Stability program or stability commitment
(c) Stability data
(d) Stability studies conclusion and proposed storage and transportation conditions

2.4.P Finished Immunogenic Product (Name, Manufacturer)

2.4.P.1 Description and Composition

(a) Description of the finished immunogenic product
(b) Composition of the finished immunogenic product

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quant. per unit or per mL	%	Quant. per unit or per mL	%	Quantity per unit or per mL	%
<complete with appropriate titles							
Subtotal 1							
<complete with appropriate title							
Subtotal 2							
Total							

(c) Type of container closure system used for the FPP and accompanying reconstitution diluents, if applicable:

2.4.P.2 Pharmaceutical Development

12.4. P.2.1 Compatibility of Immunogenic Substance with other components
13.4. P.2.2 Adjuvant, preservative, stabilizers, and excipients
13.4. P.2.3 Development of the manufacturing process
13.4. P.2.4 Container closure system

2.3.P.3 Manufacture processes of the finished immunogenic product

2.4.P.3.1 Manufacturer(s)

(a) Name, address and responsibility (e.g. fabrication, packaging, labelling, and testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing:

Name and address (include block(s)/unit(s))	Responsibility

(b) Manufacturing authorization, marketing authorization and, where available, WHO-type certificate of GMP (GMP information should be provided in *Module 1*):

2.4.P.3.2 Batch Formula

Largest intended commercial lot size:
Other intended commercial lot sizes:

(a) List of all components of the finished immunogenic product to be used in the manufacturing process and their amounts on a per batch basis;

2.4.P.3.3 Description of the manufacturing process
(a) Flow diagram of the manufacturing process
(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

2.4.P.3.4 Controls of Critical Steps and Intermediates
(a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Step (e.g. granulation, compression, coating)	Controls (parameters/limits/frequency of testing)

2.4.P.3.5 Validation and/or evaluation of the processes
2.4.P.3.6 Description of the batch identification system

12.4.P.4 Control of the adjuvant, preservative, stabilizers, and excipients

2.4. P.4.1 Specifications

(a) Summary of the specifications

2.4.P.4.2 Analytical Procedures

Summary of the analytical procedures for supplementary tests

2.4.P.4.3 Validation of Analytical Procedures

(a) Summary of the validation information for the analytical procedures for supplementary tests (where applicable)

2.4.P.4.4 Justification of Specifications

(a) Justification of the specifications (e.g. evolution of tests, analytical procedures and acceptance criteria, exclusion of certain tests, differences from officially recognized compendial standard(s)):

2.4.P.4.5 Excipients of Human or Animal Origin

(a) For FPPs using excipients without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

(b) CEP(s) demonstrating TSE-compliance can be found in:

2.4.P.4.6 Novel Excipients

2.4.P.5 Control of finished immunogenic product

2.4.P.5.1 Specifications of the immunogenic product

2.4.P.5.2 Analytical Procedures

(a) Summary or references to analytical procedures

2.4.P.5.3 Validation of Analytical Procedures

(a) Summary or references to the validation information

2.4.P.5.4. Lot consistency and analysis

(a) Description of the lots:

Strength and batch number	Batch size	Date and site of production	Use (e.g clinical, comparability studies etc)

2.4.P.5.5 Characterization and/or determination of impurities

2.4.P.5.6 Justification of Specification(s)

2.4.P.5.7 Analytical certificates

2.4.P.6 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) *not* discussed in 3.2.S.5:

(b) Characterization and evaluation of non-official primary reference

(c) Description of the process controls of the secondary reference standard

2.4.P.7 Container Closure System

(a) Description of the container closure systems, including unit count or fill size, container size or volume:

Description (including materials of construction)	Strength/concentration	Unit count or fill size	Container size (e.g. 1ml, 2ml, 5ml, etc.)

2.4.P.8 Stability of the Finished Immunogenic Product

2.4.P.8.1 Protocols and results of the stability study that justify the proposed validity period.

(a) Summary of accelerated and long-term testing parameters (e.g. studies conducted):

Storage conditions (◦C, % RH)	Strength and batch number	Batch size	Container closure system	Completed (and proposed) test intervals

(b) Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):

Container closure system	Storage statement	Shelf-life

2.4.P.8.2 Post-approval stability program

(a) Stability protocol for *Primary stability batches*, Commitment batches and Ongoing batches

13.4. P.8.3 Stability Data

(b) The actual stability results should be provided in *Module 3*.

(c) Summary of analytical procedures and validation information for those procedures *not* previously summarized in 2.3.P.5 (e.g. analytical procedures used only for stability studies):

(d) Data to support freeze thaw cycles recommended

2.4.P.8.4 Description of the procedures used to guarantee the cold chain

DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
24 Nov. 2019	0	PAR/GDL/021	Juliet A. Okecho Mutyaba Michael Etuko Daniel Kemigisha Agnes Grant Munkwase	First Issue

End of Document