



Document No.: MA/GUD/001

Guidelines for Guidelines on Vaccines: Quality, Non-Clinical and Clinical Requirements

Page 1 of 28



Zambia Medicines Regulatory Authority

**GUIDELINES APPLICATION FOR MARKETING AUTHORISATION OF
A VACCINE FOR HUMAN USE**

Contact details:

Head Office, Plot No 2350/M, Off Kenneth Kaunda International Airport Road
P.O. Box 31890, Lusaka, ZAMBIA
Tel: +260 211 220429,
E-mail: pharmaev@zamra.co.zm;
Website: www.zamra.co.zm

	Name	Designation	Signature	Date
Prepared by	Mr. Lyoko Nyambe	Director-Marketing Authorisation		25/09/2026
Reviewer	Mr. Makomani Siyanga	Director-General		25/09/2026
Approver	Hon Prof. Roma Chilengi, MP	Minister of Health		06.10.26

Version 1.0

ORIGINAL

06 OCT 2026

SIGN:.....

**Table of Contents**

1.0 ABBREVIATIONS	3
2.0 GLOSSARY	6
3.0 INTRODUCTION	8
3.1 Background.....	8
4.0 OBJECTIVES	9
5.0 SCOPE	10
6.0 QUALITY	10
7.0 NON-CLINICAL EVALUATION	11
7.1 Table of Contents of CTD Module 4.....	11
7.2 Study Reports	11
7.2.1 Pharmacology	12
7.2.2 Pharmacokinetics	13
7.2.3 Toxicology	15
7.3 Literature References.....	16
8.0 CLINICAL STUDIES	17
8.2 Table of Contents of Module 5.....	17
8.3 Tabular Listing of All Clinical Studies.....	18
8.4 Clinical Study Reports.....	18
8.4.1 Reports of Biopharmaceutical Studies	18
8.4.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	18
8.4.3 Reports of Human Pharmacokinetic (PK) Studies	18
8.4.4 Reports of Human Pharmacodynamic Studies	19
8.4.6 Reports of Post-Marketing Experience	20
8.4.7 Case Report Forms and Individual Patient Listings (when submitted)	20
8.5 Literature References.....	20
9.0 References:	21

**1.0 ABBREVIATIONS**

AEFIs – Adverse events following Immunisation

BCG – Bacillus Calmette–Guérin vaccine

COVID -19 – Corona Virus Disease of 2019

CTD – Common Technical Document

DNA – Deoxyribonucleic acid

DT – Diphtheria Tetanus

EMA – European Medicines Agency

HIV – Human Immunodeficiency Virus

HPV – Human Papiloma Virus Vaccines

ICH – International Conference on Harmonisation

IPV – Inactivated Polio Vaccine

MA – Marketing Authorisation

MAH – Marketing Authorisation Holder

MMR – Measles, mumps, and rubella (German measles).

MR – Measles, Rubella

OPV – Oral Polio Vaccine

PD – Pharmacodynamics

PK – Pharmacokinetics

PMF – Plasma master file

PSUR – Periodic Safety Update Report

PV – Pharmacovigilance

RMP – Risk Management Plan

VAMF – Vaccine Antigen Master File

WHO – World Health Organisation

ZAMRA – Zambia Medicines Regulatory Authority



Document No.: MA/GUD/000

**Guidelines for Guidelines On Vaccines: Quality, Non-Clinical And
Clinical Requirements**

Page 4 of 28



Document No.: MA/GUD/000

**Guidelines for Guidelines On Vaccines: Quality, Non-Clinical And
Clinical Requirements**

Page 5 of 28

FOREWORD

Version 1.0



2.0 GLOSSARY

Adjuvants: Substances that are intended to enhance relevant immune response and subsequent clinical efficacy of the vaccine.

Adverse event (AE): any untoward medical occurrence in a participant in a clinical trial. An AE does not necessarily have a causal relationship with the vaccine

Adverse event following immunization (AEFI): any untoward medical occurrence that follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The AEFI may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. In clinical trial documentation AEFI may often be shortened to AE.

Animal model/ relevant animal model: An animal that develops an immune response similar to the expected human response after vaccination. It is acknowledged that species-specific differences in immune responses are likely. Ideally, the animal species chosen should be sensitive to the pathogenic organism or toxin under consideration.

Booster dose(s): a dose that is given at a certain interval after completion of the primary series that is intended to boost immunity to, and therefore prolong protection against, the disease that is to be prevented

Pharmacovigilance: pharmacovigilance encompasses the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Immunogenicity: the capacity of a vaccine/adjuvanted vaccine to induce antibody-mediated immunity, cell-mediated immunity and/or immunological memory.

In vitro studies: refers to studies that are conducted in a laboratory environment using components (e.g. serum, cells or tissues) that were originally obtained from a living organism.

In vivo studies: refers to studies that are conducted with living organisms.

Nonclinical evaluation of vaccines: All in vivo and in vitro testing performed before and during clinical development of vaccines. The potential toxicity of a vaccine should be assessed not only prior to initiation of human trials, but throughout clinical development. Plasmid Double-stranded circular DNA molecules capable of replicating in bacterial cells.

Pharmacovigilance: pharmacovigilance encompasses the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Version 1.0



Plasmid: Double-stranded circular DNA molecules capable of replicating in bacterial cells.

Potency: The measure of biological activity, using a suitable quantitative biological assay, based on the attribute of the product that is linked to the relevant biological properties.

Route of administration: The means by which the candidate vaccine product is introduced to the host. Possible routes of administration include the intravenous, intramuscular, subcutaneous, transcutaneous, intradermal, transdermal, oral, intranasal, intranodal, intravaginal and intrarectal routes.

Vaccine antigen: the active ingredient in a vaccine (or generated by a vaccine) against which a specific immune response is raised. The vaccine antigen may be a live, attenuated preparation of bacteria, viruses or parasites; inactivated (killed) whole organisms; crude cellular fractions or purified antigens, including recombinant proteins (i.e. those derived from recombinant DNA/RNA expressed in a host cell); polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/ or toxoids, synthetic antigens, or heterologous proteins expressed by plasmid DNA or viral or bacterial vectors. It may also be a combination of the antigens or immunogens listed above.

Vaccine efficacy: vaccine efficacy measures direct protection (that is, protection induced by vaccination in the vaccinated population sample). Vaccine efficacy is most commonly a measure of the proportionate reduction in disease attack rate (AR) between the control group that did not receive vaccination against the infectious disease under study (ARU) and the vaccinated (ARV) group(s). Vaccine efficacy can be calculated from the relative risk (RR) of disease among the vaccinated group as $(ARU - ARV/ARU) \times 100$ and $(1 - RR) \times 100$. This estimate may be referred to as absolute vaccine efficacy. Alternatively, vaccine efficacy may be defined as a measure of the proportionate reduction in disease AR between a control group that is vaccinated against the infectious disease under study and the group vaccinated with the candidate vaccine. This estimate may be referred to as relative vaccine efficacy.



3.0 INTRODUCTION

3.1 Background

Recent progress in biotechnology and basic immunology has led to the development of a broad range of novel vaccines raising exciting possibilities for the prevention of infectious diseases. Improvements to already licensed vaccines are also being considered; such improvements will lead to new products as well as to the introduction of new adjuvants. However, the complexity and novelty of these products presents scientific and regulatory challenges because criteria for their safety, potency and quality assessment may not exist [1].

The regulation of vaccines can be divided into three stages: developmental, grant of Marketing Authorisation and Post Marketing Authorisation activities. The developmental stage consists of two parts namely; preclinical research and development, and clinical research and development [1]. On the other hand, Marketing Authorisation means grant of Marketing Authorisation for the placement of a medicine or allied substance on the market while Post Marketing Authorisation is the identification and collection of information regarding medicines after their authorisation for use in a population.

Non-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 of the product in humans. Product diversity and new approaches, technologies and methodologies develop over time; therefore, judgement based on the best science available should always form the basis for deciding on the type and extent of nonclinical evaluation for these products [1]. Although nonclinical evaluation plays an essential part in the overall development of vaccine candidates, there is at present limited guidance regarding nonclinical evaluation programs for these products. Nonclinical evaluation, within the context of this document, refers to all in vivo and in vitro testing performed before and during the clinical development of vaccines. For example, nonclinical evaluation may be necessary when changes in the manufacturing process or product formulations are made or to further study potential safety concerns that may have arisen from phase I and II trials or that have been described in the literature for similar products [1].

The section on clinical evaluation of vaccines covers the design of clinical development programs for vaccines that are intended to provide pre- and post-exposure prophylaxis as well as therapeutic treatment against infectious diseases such as Ebola. Some of the guidance provided is also relevant to the further development of licensed vaccines (i.e. generation of clinical data to support changes to the prescribing information in the post-authorisation period).

In the development of any new vaccine adequate data on immunogenicity should be assembled during the clinical development program. Some of the areas that should usually be covered include characterisation of the immune response, investigation of an appropriate dose and primary



schedule, assessment of the persistence of detectable immunity and consideration of the need for and response to booster doses.

In this guidance document, the general principles of quality, nonclinical and clinical evaluation of vaccines are discussed, with particular attention being given to the regulatory expectations for new and novel vaccines.

4.0 OBJECTIVES

These guidelines are intended to:

- Replace the 2008 “Guideline on Applications for Registration of Vaccines and other Biological Products for Human and Veterinary use”.
- Assist applicants in the preparation of quality, non-clinical and clinical modules of applications for Marketing Authorisation of vaccines in Zambia.
- Provide guidance on technical and other general requirements.
- Provide links to key product guidelines and relevant recommendations to assure quality, safety and efficacy of vaccines.



5.0 SCOPE

This guideline provides recommendations on the quality, non-clinical and clinical requirements that should be submitted in order to obtain Marketing Authorisation of a vaccine intended for human use in pre- and post- exposure prophylaxis, and in some cases, indicated for therapeutic treatment. Both prophylactic and therapeutic vaccines for infectious disease indications are considered in this document. This guideline is intended for all types of vaccines including simple vaccines, vaccines produced by recombinant DNA technology, single component vaccines, multicomponent (combined) vaccines, cellular and acellular etc., entering the Marketing Authorisation procedure. In addition, the principles laid down in the guideline should be considered by applicants entering into clinical trials.

All other issues common to the design, conduct and evaluation (assessment) of human challenge trials in vaccine development may be found in “WHO guideline in Human Challenge trials for vaccine development: regulatory considerations” [2].

This guideline should be read in conjunction with all relevant current guidelines pertaining to marketing authorization of medicinal products, vaccines and individual vaccine specific recommendations. A non-exhaustive list of other relevant guidelines is provided in annex 1.0. As new guidelines maybe developed by WHO and other reference regulatory authorities, applicants are encouraged to ensure that such prevailing guidelines are consulted.

6.0 QUALITY

Submission of the quality part of the application should be made as per *ZAMRA* Guidance on Submission of Applications for Marketing Authorisation in Common Technical Document Format: Quality [3]. The quality evaluation should at the minimum cover information on the drug substance including structure, manufacturing, characterization, control of the drug substance, reference materials, container closure system and stability. Information on the drug product should include description and composition, pharmaceutical development, manufacture, control of excipients, control of the drug product, reference standards, container closure system and stability.

Facilities and equipment information should be included in module 3.2.A.1 and a comprehensive evaluation of adventitious agents should be provided in module 3.2.A.2. This should cover all components derived from animals and human beings.

Where a Certificate of Vaccine Antigen Master File (VAMF) or Certificate of Plasma Master File (PMF) exists, such documents should be provided in Module 1.



7.0 NON-CLINICAL EVALUATION

Nonclinical studies should comply with the WHO's Guidelines on Nonclinical Evaluation of Vaccines, WHO Technical Report Series No. 927, 2005[1] or the most recent version. In addition, vaccines containing adjuvants should comply with the WHO Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines. Additional information for the preparation of this section can be found in ICH safety ICH M4S (R2) [4] and Note for Guidance on Repeated Dose Toxicity CPMP/SWP/465/95 [5].

7.1 Table of Contents of CTD Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

7.2 Study Reports

The study reports should be presented in the following order:

7.2.1 Pharmacology.

- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions

7.2.2 Pharmacokinetics

- Analytical Methods and Validation Reports (if separate reports are available)
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions (non-clinical)
- Other Pharmacokinetic Studies

7.2.3 Toxicology

- Single-Dose Toxicity (in order by species, by route)
- Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- Genotoxicity
 - In vitro
 - In vivo (including supportive toxicokinetics evaluations)
- Carcinogenicity (including supportive toxicokinetics evaluations)



- Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Other studies
- Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
 - Fertility and early embryonic development
 - Embryo-fetal development
 - Prenatal and postnatal development, including maternal function
 - Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
 - Local Tolerance
- Other Toxicity Studies (Where other toxicity studies have been performed the reports should be provided in the relevant sections below)
 - Antigenicity
 - Immunotoxicity
 - Mechanistic studies (if not included elsewhere)
 - Dependence
 - Metabolites
 - Impurities
 - Any other significant parameter on toxicity

7.2.1 Pharmacology

7.2.1.1 Primary Pharmacodynamics

A pharmacodynamics study for a vaccine product is generally conducted to evaluate the immunogenicity of the vaccine or, when animal models are available, the capacity of a vaccine to confer protection. The investigations should include a quantitative and qualitative evaluation of immune responses according to dose and dose interval. These data should characterise the humoral, cell mediated and innate immune responses as appropriate to both the intended protective antigen as well as to the antigens of the vector used, as the latter constitute part of the immune response to the vaccine and are important in estimating the possibility of re-use of the vector virus in another vaccine. In addition, a pharmacodynamics study may also extend to include the pharmacology of an adjuvanted vaccine to provide evidence for the need for the adjuvant.

7.2.1.2 Secondary Pharmacodynamics

Generally, not performed. If they have been performed, secondary pharmacodynamic studies should be briefly summarised in this section.

7.2.1.3 Safety Pharmacology

Version 1.0



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

7.2.1.4 Pharmacodynamic Drug Interactions

Generally, not performed. If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.

7.2.2 Pharmacokinetics

Generally, not performed for vaccines; however, biodistribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors. The feasibility of such studies should be evaluated on a case-by-case basis. Where pharmacokinetic studies have been performed, the study reports should be provided in the relevant sections below:

- Brief Summary
- Analytical Methods and Validation Reports (if separate reports are available)
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions (nonclinical)
- Other Pharmacokinetic Studies

7.2.2.1 Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasizing, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

7.2.2.2 Analytical Methods and Validation Reports

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

Version 1.0



7.2.2.3 Absorption

The following data should be summarised in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies)

7.2.2.4 Distribution

The following data should be summarised in this section:

- Tissue distribution studies
- Protein binding and distribution in blood cells
- Placental transfer studies

7.2.2.5 Metabolism (interspecies comparison)

The following data should be summarised in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Pre-systemic metabolism (Gastrointestinal (GI) /hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition.

7.2.2.6 Excretion

The following data should be summarised in this section:

- Routes and extent of excretion
- Excretion in milk and other body fluids

7.2.2.7 Pharmacokinetic Drug Interactions

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarised in this section.

7.2.2.8 Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarised in this section.

7.2.2.9 Discussion and Conclusions

This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.

7.2.2.10 Tables and Figures

Text tables and figures can be included in appropriate sections throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.



7.2.3 Toxicology

7.2.3.1 Single-Dose Toxicity

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

7.2.3.2 Repeat-Dose Toxicity

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

7.2.3.3 Genotoxicity

Generally, not performed for vaccines. However, where required (e.g if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity) these shall be submitted. Where genotoxicity studies have been performed, the reports should be provided in the relevant sections below:

- *in vitro* non-mammalian cell system
- *in vitro* mammalian cell system
- *in vivo* mammalian system (including supportive toxicokinetics evaluation)
- other systems

7.2.3.4 Carcinogenicity (including toxicokinetics)

Generally, not performed for vaccines. However, where required (e.g if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity) these shall be submitted. Where carcinogenicity studies have been performed, the reports should be provided in the relevant sections below:

- Long-term studies (not included in repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (not included under repeat-dose toxicity or pharmacokinetics)
- Other studies

7.2.3.5 Reproductive and Developmental Toxicity

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, if the target population for the vaccine includes pregnant women and women of childbearing potential, developmental toxicity studies should be considered unless a scientific and clinically sound argument is put forward by the manufacturer to show that conducting such studies is unnecessary. Where reproductive and developmental toxicity studies have been performed, the reports should be provided in the relevant sections below:



- Fertility and early embryonic development
- Embryo-fetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
- Local Tolerance

The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study. Reference should be made to Guidelines on Non-clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00) [6].

7.2.3.7 Other Toxicity Studies (if available)

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

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not included elsewhere)
- Dependence
- Metabolites
- Impurities
- Other studies

7.3 Literature References

All literature references cited including all in-house protocols used should be provided.



8.0 CLINICAL STUDIES

8.1 Regulatory Expectations

A Clinical Trial Application is required for studies conducted in Zambia. Sponsors should refer to Guidelines for the Authorisation of Clinical Trials of Medicines, Nutritional Supplements, Vaccines and Medical Devices in Zambia [7].

The WHO recommendations applicable to the specific vaccine should also be considered as well as other national and international regulatory guidelines. Sponsors may refer to the most up to date version of the WHO Guidelines on Clinical Evaluation of Vaccines[8]. Information for the preparation of this section can be found in ICH M4E Common technical document for the registration of pharmaceuticals for human use – Efficacy [9], ICH E3 Guideline on Structure and Content of Clinical Study Reports [10] and ICH E6 (R2) Guideline for Good Clinical Practices [11].

Clinical trials in humans are generally classified into three or more Phases (Refer to the Guidelines for the Authorisation of Clinical Trials in Zambia [7] and formal regulatory approval is required to undertake any of these studies. This is in addition to ethical clearance which is required for clinical trials in all countries.

Ideally, by the beginning of the Phase III stage of development, a vaccine should have been fully characterised and the final manufacturing process, specifications and batch release testing procedures should have been established. Additional information may be required to support quality changes made post-Phase III studies [12].

An application for grant of Marketing Authorisation may be submitted to ZAMRA on the basis of the data from Phase III testing and, if approved, the vaccine then becomes commercially available.

The structure of the clinical development programme must be tailored to the type of vaccine and the antigenic content. For example, the clinical evaluation of a vaccine that contains only novel antigen(s) may of necessity be very different from that of a vaccine that contains one or more previously evaluated antigens. Such factors also influence whether clinical protection trials will be required, whether or not they are feasible, or whether an approval may reasonably be based on immunogenicity data only. In all instances, it is the obligation of the applicant to justify the content and structure of the clinical development programme. Pre-submission meetings with regulatory authorities may assist in ensuring that the content of the final data package is likely to be acceptable [12].

8.2 Table of Contents of Module 5

A Table of Contents should be provided that lists all of the clinical study reports and gives the location of each study report in the Common Technical Document.

**8.3 Tabular Listing of All Clinical Studies**

A tabular listing of all clinical studies and related information should be provided (e.g. type of study, study identifier, location of study report in the application, study objectives, study design and type of control, dosage regimen, route of administration, number and type of subjects, study status e.t.c). The sequence in which the studies are listed should follow the sequence described in section 8.4 below.

8.4 Clinical Study Reports

Clinical study reports should be provided in the relevant sections below. Additional information on the structure and content of the Clinical Study Report can be found in the ICH E3 Guideline [10].

8.4.1 Reports of Biopharmaceutical Studies

Biopharmaceutical studies are not generally performed for vaccines. If they have been performed, biopharmaceutical studies should be briefly summarised in this section.

- Bioavailability Study Reports
- Comparative Bioavailability and Bioequivalence Study Reports
- In vitro – In vivo Correlation Study Reports
- Reports of Bioanalytical and Analytical Methods for Human Studies

When immunogenicity studies are conducted, reports of bioanalytical assay results should be provided in section 8.4.5.

8.4.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

Not generally performed for vaccines. If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.

- Plasma Protein Binding Study Reports
- Reports of Hepatic Metabolism and Drug Interaction Studies
- Reports of Studies Using Other Human Biomaterials

8.4.3 Reports of Human Pharmacokinetic (PK) Studies

Not generally performed for vaccines. If they have been performed, Human Pharmacokinetic studies should be briefly summarised in this section.

- Healthy Subject PK and Initial Tolerability Study Reports
- Patient PK and Initial Tolerability Study Reports
- Intrinsic Factor PK Study Reports
- Extrinsic Factor PK Study Reports
- Population PK Study Reports

**8.4.4 Reports of Human Pharmacodynamic Studies**

For vaccines, the immunogenicity studies are usually conducted to support the selection of dose, dosage schedule, and formulation of the final product, and the study reports should be provided in Section 8.4.5.

- Healthy Subject PD and PK/PD Study Reports
- Patient PD and PK/PD Study Reports

8.4.5 Reports of Efficacy and Safety Studies

Reports of all clinical studies designed to assess the efficacy and safety of the vaccine conducted by the sponsor (or otherwise available), including all completed and all ongoing studies of the vaccine in proposed and non-proposed indications, should be provided in the relevant sections below. This should include the reports of the immunogenicity studies conducted to support the selection of dose, dosage schedule, and formulation of the final product.

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

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

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

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

8.4.5.2 Study Reports of Uncontrolled Clinical Studies

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

8.4.5.3 Reports of Analyses of Data from More than One Study

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

8.4.5.4 Other Study Reports

This section can include the following:

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

Version 1.0



- Development Safety Update Reports

8.4.6 Reports of Post-Marketing Experience

Relevant post-marketing studies or information (including all significant safety observations) should be included here. A Pharmacovigilance Plan and consolidated report on Adverse Events following immunization (AEFIs) in line with ICH E2E [12], which at minimum should include the following:

- An organogram showing organisation of the PV unit and location
- Responsibilities of MAH, local responsible person etc.
- Summary of on-going safety issues or routine update reports
- Proposed routine Pharmacovigilance practices
- Action plan for safety and reports e.g. PSUR etc.
- Risk Management Plan (RMP).
- Updates on on-going post-marketing studies

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

Case report forms and individual patient data listings that are described in appendices 16.3 and 16.4 in the ICH E3 guideline [10] should be placed in this section, when submitted. They should be presented in the same order as the clinical study reports and indexed by study.

8.5 Literature References

This section should include copies of all references cited in the Clinical Overview and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3.

**9.0 References:**

1. WHO's Guidelines on Nonclinical Evaluation of Vaccines, WHO Technical Report Series No. 927, 2005 Annex
https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%20Nonclinical.P31-63.pdf?ua=1
2. WHO guideline in Human Challenge trials for vaccine development: regulatory considerations
https://www.who.int/biologicals/expert_committee/Human_challenge_Trials_IK_final.pdf
3. ZAMRA Guidance on Submission of Applications for Marketing Authorisation in Common Technical Document Format: Quality. 2016 <http://www.zamra.co.zm/wp-content/uploads/2016/10/GUIDANCE-FOR-THE-PREPARATION-AND-SUBMISSION-OF-DOSSIERS-IN-COMMON-TECHNICAL-DOCUMENT-FORMAT-QUALITY.pdf>
4. ICH Safety – M4S(R2) Nonclinical Overview and Nonclinical Summaries of Module 2 Organisation of Module 4
https://database.ich.org/sites/default/files/M4S_R2_Guideline.pdf
5. Note for Guidance on Repeated Dose Toxicity (CPMP/SWP/465/95), 27th July 2000 https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-repeated-dose-toxicity_en.pdf
6. Guidelines on Non-clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00)
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-local-tolerance-testing-medicinal-products_en.pdf
7. Guidelines for the Authorisation of Clinical Trials of Medicines, Nutritional Supplements, Vaccines and Medical Devices in Zambia
<http://www.zamra.co.zm/wp-content/uploads/2016/10/Guidelines-on-Application-for-Clinical-Trial-Authorisation.pdf>



8. Guideline on Clinical Evaluation of New Vaccines EMEA/CHMP/VWP/164653/2005
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-new-vaccines_en.pdf
9. ICH Efficacy – M4E(R2) M4E(R2) - Common technical document for the registration of pharmaceuticals for human use – Efficacy
https://database.ich.org/sites/default/files/M4E_R2_Guideline.pdf
10. ICH E3 Guideline on Structure and Content of Clinical Study Reports.
<https://www.ema.europa.eu/en/ich-e3-structure-content-clinical-study-reports>
11. ICH E6 (R2) Guideline for Good Clinical Practices. <https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice>
12. ICH E2E Pharmacovigilance Planning (Pvp)
https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-25.pdf

**Annex 1****List of vaccine specific guidelines**

No	Vaccine	Guideline/Recommendation
1.	BCG: BCG Vaccine	Recommendations to assure the quality, safety and efficacy of BCG vaccines, Annex 3, TRS No.979 31 January 2013
2.	Cholera: inactivated oral	Guidelines for the production and control of inactivated oral cholera vaccines Annex 3, TRS No. 924 19 November 2004
3.	DNA vaccines	Guidelines on quality, safety and efficacy of plasmid DNA Vaccines Annex 2, TRS No.1028 10 March 2021 Guidelines for assuring the quality and non-clinical safety of DNA Vaccines, Annex 1, TRS 941 2007
4.	Dengue Tetravalent (live, attenuated)	Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated), Annex 2, TRS No 979
5.	Diphtheria	Recommendations to assure quality, safety and efficacy of diphtheria vaccines (adsorbed), Annex 4, TRS No 980 2014
6.	Diphtheria-Tetanus	Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines, Technical Report Series 980, 2014



7.	Diphtheria-Tetanus-Pertussis (acellular)	WHO Manual for Quality Control of Diphtheria, Tetanus and Pertussis Vaccines
8.	Diphtheria-Tetanus Pertussis (acellular)-Hepatitis B- <i>Haemophilus influenza</i> type b-Polio (Inactivated)	Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines Replacement of Annex 2 of WHO Technical Report Series, No. 800
9.	Diphtheria-Tetanus-Pertussis (whole cell)	Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines Replacement of Annex 2 of WHO Technical Report Series, No. 800
10.	Diphtheria-Tetanus-Pertussis (whole cell)- <i>Haemophilus influenza</i> type b	Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines Replacement of Annex 2 of WHO Technical Report Series, No. 800
11.	Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B	Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines Replacement of Annex 2 of WHO Technical Report Series, No. 800
12.	Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B- <i>Haemophilus influenza</i> type b	Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines Replacement of Annex 2 of WHO Technical Report Series, No. 800
13.	Ebola	Guidelines on the quality, safety and efficacy of Ebola Vaccines, WHO TRS 1011, Annex 2 17 July 2018
14.	Enterovirus	Recommendations to assure the quality, safety and efficacy of enterovirus 71 vaccines (inactivated), Annex 2, TRS No. 1030 11 May 2021
15.	COVID - 19	EMA considerations on COVID 19 vaccine approval USFDA Guidance for Industry on Development and Licensure of Vaccines to Prevent COVID-19
16.	<i>Haemophilus influenza</i> type b	Recommendations for the production and quality control of <i>Haemophilus influenza</i> type b conjugate vaccines, TRS No.897, 2000



17.	Hepatitis A (Human Diploid Cell), Inactivated (Adult)	Requirements for Hepatitis A Vaccines (Inactivated), Annex 2, TRS No.858
18.	Hepatitis B	Requirements for Hepatitis B Vaccine prepared from Plasma, Annex 8, Technical Report Series No. 771, 1988
19.	Hepatitis E	Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines, Annex 2, TRS 1016
20.	Human Papillomavirus (Bivalent)	Recommendations to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines, Technical Report Series, No. 999, Annex 4
	Human Papillomavirus (Quadrivalent)	Recommendations to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines, Technical Report Series, No. 999, Annex 4
21.	Influenza	Recommendations for the production and control of influenza vaccine (inactivated), WHO Technical Report Series No. 927, Annex 3 Recommendations to assure the quality, safety and efficacy of influenza vaccines (human, live attenuated) for intranasal administration Annex 4, TRS No 977 Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries, Annex 7, TRS No 1004
22.	Japanese Encephalitis Vaccine (Inactivated)	Recommendations to assure the quality, safety and efficacy of Japanese encephalitis vaccines (live, attenuated) for human use, Technical Report Series 980, 2012
23.	Malaria	Guidelines on the quality, safety and efficacy of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of <i>Plasmodium falciparum</i> Annex 3, TRS No 980 2014
24.	Measles	Requirements for measles, mumps and rubella vaccines and combined vaccine (live), Technical Report Series No. 840, 1994, Annex 3
25.	Measles and Rubella (MR)	Requirements for measles, mumps and rubella vaccines and combined vaccine (live), Technical Report Series No. 840, 1994, Annex 3



26.	Measles, Mumps and Rubella (MMR)	Requirements for measles, mumps and rubella vaccines and combined vaccine (live), Technical Report Series No. 840, 1994, Annex 3
27.	Meningococcal A Conjugate	Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines, TRS 962, Annex 2
28.	Meningococcal A+C	Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines, TRS 962, Annex 2
29.	Meningococcal ACYW-135 (conjugate vaccine)	Recommendations for the production and control of Meningococcal group C conjugate vaccines, TRS 924,2004, ANNEX 2
30.	Meningococcal ACYW-135 (polysaccharide)	Requirements for meningococcal polysaccharide vaccine (Amendment 1999) TRS 904, Annex 2
31.	Pertussis	Recommendations for whole cell pertussis vaccine, Annex 6, TRS No 941
		Recommendations to assure the quality, safety and efficacy of acellular pertussis vaccines Annex 4, TRS No 979
32.	Pneumococcal (conjugate)	WHO recommendations to assure the quality, safety and efficacy for pneumococcal conjugated vaccines, Annex3, Technical Report Series 977,2009. Replacement of WHO Technical Report Series ,927, Annex 2
33.	Polio Vaccine - Inactivated (IPV)	Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated) Annex 3, TRS 1024 2020
34.	Polio Vaccine - Oral (OPV)	Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) TRS980, 2012
35.	Rabies	Recommendations for inactivated rabies vaccine for human use produced in cell substrates and embryonated eggs, TRS941, 2007, Annex 2
36.	Respiratory Syncytial Virus	Guidelines on the quality, safety and efficacy of Respiratory Syncytial Virus Vaccines, Annex 2, TRS No 1024
37.	Rotavirus	Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines (oral), TRS 941, Annex 3
38.	Rubella	Requirements for measles, mumps and rubella vaccines and combined vaccines, live TRS No.840, Annex 3



39.	Synthetic Peptides	Guidelines for the production and quality control of synthetic peptide vaccines, Annex 1, TRS No 889
40.	Smallpox	Recommendations for the production and quality control of smallpox vaccine, revised 2003, Annex 1, TRS No 926
41.	Tetanus Toxoid	Annex 5 Recommendations to assure the quality, safety and efficacy of tetanus vaccines (adsorbed) Replacement of Annex 2 of WHO Technical Report Series, No. 800, and Annex 5 of WHO Technical Report Series, No. 927
42.	Typhoid	Typhoid polysaccharide vaccine, Title: Requirements for Vi polysaccharide typhoid vaccine; adopted 1992 TRS No 840, Annex 1. Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines WHO TRS,987, Annex 3
43.	Varicella	Requirements for Varicella Vaccine (Live); Revised 1993, TRS No 848, Annex 1
44.	Yellow Fever	Yellow fever virus, production and testing of WHO primary seed lot 213-77 and reference batch 168-736 Recommendations to assure the quality, safety and efficacy of live attenuated Yellow Fever vaccines. Replacement of Annex2 of WHO TRS 872 and the amendment to that annex in WHO TRS 964 (2012)

Other General Guidelines for Various Vaccines

1. WHO good manufacturing practices for biological products
https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf
2. Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks
https://www.who.int/biologicals/vaccines/TRS_978_Annex_3.pdf



Document No.: MA/GUD/000

**Guidelines for Guidelines On Vaccines: Quality, Non-Clinical And
Clinical Requirements**

Page 28 of 28