



PHARMACEUTICAL REGULATORY AUTHORITY

**GUIDELINES ON APPLICATIONS
FOR REGISTRATION OF VACCINES
AND OTHER BIOLOGICAL
PRODUCTS
FOR HUMAN AND VETERINARY USE**

First Edition

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Foreword

The Pharmaceutical Act (No. 14) of 2004 requires that pharmaceutical products including vaccines and other biological medicinal products intended to be marketed in Zambia meet acceptable standards of quality, safety and efficacy and at the same time be assessed to have been manufactured in facilities which comply with current Good Manufacturing Practices (cGMP).

These guidelines have been developed to provide requirements in support of quality, safety and efficacy in respect of vaccines and other biological medicinal products meant to be placed on the Zambian market.

One of the means for ensuring that products meet the required standards of quality, safety and efficacy is by conducting product specific pre-marketing assessments to determine whether the product should be registered.

Submission of adequate documentation on quality, safety and efficacy of a vaccine and other biological medicinal product will enable the Pharmaceutical Regulatory Authority (PRA) to use the information and other factors to assess the suitability of the product for the intended use.

Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the applications and subsequent registration of the products. This will enable the product prospective licence holders to market their products on time and make them available to the consumers in a timely manner.

It is therefore my sincere hope that these guidelines will provide the necessary information in preparing and submitting documents for registration of vaccines and other biological medicinal products in Zambia.

Finally, I wish to urge our esteemed readers and applicants to read this edition of guidelines carefully and make as many suggestions as possible so that we have a version of the guidelines that are commensurate with current practices.

Dr S.K. Miti
PERMANENT SECRETARY
Ministry of Health

Acknowledgements

The Ministry of Health (MoH) and the Pharmaceutical Regulatory Authority (PRA) wish to acknowledge the immense contributions of individuals and organisations that constituted the Technical Working Group in developing these guidelines. The principal contributors for this guidance document were:

1. Dr. Ray Handema: National Institute for Scientific & Industrial Research
2. Ms Esnat Mwape: Director General, PRA
3. Dr Bernard Hang'ombe: Lecturer, UNZA School of Veterinary Medicine
4. Ms Violet Kabwe: International Consultant, Lusaka
5. Mr Kapindula : Environmental Council of Zambia
6. Ms Anne Zulu: Pharmacist, Medical Stores Limited
7. Mrs Caroline M. Yeta: Director-Inspectorate & Licensing
8. Dr K Choongo: Lecturer, UNZA School of Veterinary Medicine
9. Ms Loyce Lishimpi: National Profession Officer, WHO
10. Mrs Bernice C. Mwale: Director-Product Registration, PRA,
11. Mr. Felix P. Chizu: Regulatory Officer, PRA
12. Dr Zuma Munkombwe: Regulatory Officer, PRA
13. Mr. Pelekelo Mangisha: Assistant Regulatory Officer, PRA

The MoH and PRA would further like to thank the World Health Organisation (WHO) for providing financial and technical support to the development of these guidelines.

Ms E. Mwape
DIRECTOR-GENERAL
Pharmaceutical Regulatory Authority

Abbreviations & Acronyms

API	- Active Pharmaceutical Ingredient
BP	- British Pharmacopoeia
BPC	- British Pharmaceutical Code
BPR	- Batch Production Record
BVP	- British Veterinary Pharmacopoeia
DNA	- Deoxyribonucleic Acid
EPC	- End of Production Cells
GMP	- Good Manufacturing Practice
IP	- International Pharmacopoeia
INN	- International Non proprietary Name
IQ	- Installation Qualification
MCB	- Master Cell Bank
MPR	- Master Production Record
OQ	- Operational Qualification
Ph.Eur	- European Pharmacopoeia
rDNA	- Recombinant Deoxyribonucleic Acid
SADC	- Southern African Development Community
PRA	- Pharmaceutical Regulatory Authority
USP	- United States Pharmacopoeia
WCB	- Working Cell Bank
WHO	- World Health Organization
cGMP	- Current good manufacturing practice
SI	-Statutory Instrument
ATC	-Anatomical Therapeutic and Chemical classification System for biologicals
OIE	- The Office international des épizooties (OIE, French for "International Epizootic Office"), now known as World Organisation for Animal Health

Definitions & Interpretations

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

Authority refers to the Pharmaceutical Regulatory Authority

Antisera refer to preparations of antibodies of animal origin intended to treat or provide immediate protection against infections.

Biologicals include *in vitro* diagnostic antigens, immunoglobulin, antisera, antitoxins and toxoid.

Diagnostic antigen is a crude or purified fraction isolated from microbial culture and intended for *in vitro* detection of an existing specific immune response, usually by intradermal or percutaneous skin testing.

Immunoglobulins are preparations of antibodies of human origin intended to treat or provide immediate protection against infections.

Vaccine an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection. A vaccine may be a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombining DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as the plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens or cells pulsed with immunogen. It may also be a combination of immunogens as listed above.

Immunogenic Substance or immunogen An 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), 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.

Biological medicinal product is the finished dosage form of the biological substance. The biological medicinal product contains the immunogenic substance(s) formulated with other ingredient in the finished dosage form ready for marketing. Other ingredients, active or inactive, may include adjuvants, preservatives, stabilizers, and/or excipients. For vaccine formulation, the immunogenic substance(s) may be diluted, adsorbed, mixed with adjuvants or additives, and/or lyophilized to become the medicinal product.

Pharmacopoeias refer to the current edition of British Pharmacopoeia(B.P), British Veterinary Pharmacopoeia, European Pharmacopoeia, (Ph.Eur), International Pharmacopoeia, (IP) , United States Pharmacopoeia, (USP) or any other pharmacopoeia identified and acceptable to the Authority

Batch/Lot means a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it can be expected to be homogenous

INTRODUCTION

The Pharmaceutical Act No 14 of 2004 requires that products intended to be marketed in Zambia meet appropriate standards of good quality, safety and efficacy. Also they should be manufactured in facilities, which comply with cGMP requirements. One of the means for ensuring that biologicals including vaccines and immunological products meet the required standards of good quality, safety and efficacy is by conducting product specific pre-marketing assessments to determine whether the product should be registered.

These Guidelines have been prepared to provide information to applicants who intend to register vaccines and other biological products in Zambia.

This document has been developed by the Pharmaceutical Regulatory Authority (PRA) to provide guidance to applicants on the content and format of the Chemistry and pharmaceutical data of such products required for their complete scientific evaluation for quality, safety and efficacy. These guidelines also indicate the order of the material to be submitted and the minimum requirements for product registration.

These Guidelines are arranged in five parts and five appendices as follows:-

- Part1: General information
 - Part2: Summary of product characteristics
 - Part 3: Chemistry, manufacturing and controls of immunogenic substances
 - Part 4: Finished Medicinal product
 - Part 5: Toxicological Data
 - Part 6: Safety and Efficacy Data
-
- Appendix I: Anatomical Therapeutic and Chemical classification system of Biologicals.
 - Appendix II: Clarifies the information required on Package insert
 - Appendix III: Labeling requirements
 - Appendix IV: Application form format
 - Appendix V: SI on fees

Applications for registration and appended documents are accepted in the format and language as specified under general requirements in these guidelines.

Applicants are advised to read carefully these guidelines and prepare appropriate applications. Submission of applications which do not comply with the prescribed requirements may result in delays in processing, issuance of queries or rejection of the applications.

PART 1
GENERAL INFORMATION

All applications shall be made by submitting a duly completed application form accompanied with fees and information as prescribed in these guidelines. All documents shall be in English. However, where original certificates are in another language, copies shall be presented together with certified English translations.

1.1 Applicants and responsible persons

1.1.1 Applicant

1.1.1.1 An application for registration of biologicals can be made by owner of the product (an individual, body corporate, partnerships or registered business) responsible for the manufacture or to whose order the product is manufactured for sale in Zambia;

1.1.1.2 The applicant shall be responsible for the product, information supplied in support of his application for registration and alterations thereof.

1.1.2 Responsible Persons

1.1.2.1 Every applicant who is not resident in Zambia shall nominate a distributor who is licensed as a pharmaceutical importer and wholesaler and resides in Zambia to be responsible local persons. Every nominee shall submit a power of attorney as evidence of nomination.

1.1.3 The responsible local distributor, licence holder and manufacturer shall:

1.1.3.1 Monitor the product on the market and inform the Authority immediately after the detection of any problem relating to a registered product such as serious manufacturing defects which may endanger public health.

1.1.3.2 Handle product recalls according to the Authority established recall procedures

1.1.4 The responsible local distributor shall facilitate communication between the applicant, licence holder and/or manufacturer and the Authority on matters relating to the product.

1.2 Applications

1.2.1 A separate application is required for each product, i.e. products containing the same ingredients but made to a different specification (in terms of strength or content of active and non active ingredients, dosage form, etc) or by a different manufacturing site

1.2.2 Products other than injectables, made by the same manufacturer to the same specifications, strength (content) of ingredients and dosage form, but differing only in pack sizes require only one application but stability report should be submitted for such different primary packaging specifications

1.2.3 Applications shall be made by submitting a duly completed application form which shall be accompanied with:

- i. Complete documentation as per these guidelines supported by independent expert reports on quality, safety and efficacy. All ingredients must comply with specifications prescribed either in the United States, European, British or International pharmacopoeias. In-house specifications may be acceptable if justified.
- ii. Original Certificate of Pharmaceutical Product (WHO type) from a National Regulatory Authority of the exporting country accompanied with approved product information.
- iii. Registration fee as prescribed in SI on fees
- iv. GMP inspection fee determined by PRA
- v. Five or more commercial samples of each package size being applied for to carry out quality control tests as declared in the dossier. The samples must be in the form and container in which they will be marketed.
- vi. An appropriate and complete index/list of the various chapters and documents of the submission.
- vii. Current Site Master File

1.2.4 Application for alteration of a registered product

Whenever a product licence holder makes any alteration to a product, s/he must apply to and obtain approval from the Authority in respect of a registered product before introducing it in Zambia. An application shall be made on an Application Form for Alteration and shall be accompanied with:

- (i) Detailed description of the alteration with supporting reasons.
- (ii) Samples of the altered product.
- (iii) Alteration fee

1.2.5 Application for renewal of Product registration

Applications for renewal of registration of products shall be submitted at least 90 days before the expiry date of registration.

Renewal of registration shall be made on a Renewal Application Form which shall be accompanied with:

- (i) Consolidated report of all changes if any (reported and unreported) which had been made with respect to product during the validity of its registration;
- (ii) Report of additional adverse event following immunization detected during the lifetime of the product;
- (iii) At least five commercial samples of each package size being applied for registration or sufficient samples to carry out quality control tests as declared in the dossier whichever is higher. The samples must be in the form and container in which they will be marketed;
- (iv) Renewal application fee;
- (v) GMP inspection fee determined from time to time by the Authority

1. 3. Documentation

1.3.1 Paper type and binding

Data shall be presented on A4 and 80g/m² paper with readily readable letters of at least 12 font sizes. Every page shall be numbered sequentially.

Extension sheets, tables, diagrams, and other supporting documents shall as far as possible be of the same size, well-annotated, numbered and appropriately referenced or cross-referenced.

All chapters must be bound separately and arranged sequentially in one or more A4 size accessible spring file covers depending on the number of pages contained in a chapter.

However whenever two or more chapters are bound in a single file, cover marked dividers should separate them. The binding shall be in such a manner as to allow chapters to be detached for evaluation by different experts.

The file cover should be of hard, non-collapsible bio-degradable material. Arch Lever files are not permissible. The thickness should be expandable or reducible depending on the total thickness of the contents.

1.3.2 Official references

When direct reference is made to specifications, quality control procedures, test methods, data etc. in official compendia, texts or standard publications other than the current pharmacopoeias, reprints or authenticated copies of relevant pages shall be enclosed. References to pharmacopoeias should specify the year of issue.

1.3.3 Expert reports

Expert reports shall accompany documentation on quality, safety and efficacy. All copies should be authenticated by authorized signatories and stamped officially.

1.3.4 Manuals

An applicant may have several products which are pharmaceutically similar and the same data may be applicable to these products e.g. specifications for named ingredients, standard analytical methods or test protocols.

In order to avoid unnecessary duplication, this information may be assembled in the form of a manual e.g. "Manual – Specifications for Ingredients" or "Manual – Analytical Methods and Test Protocols".

One hard copy of a manual and a CD-ROM if any should be submitted together with the first application. In subsequent applications appropriate reference may then be made to these "Manuals".

Such manuals must be clearly headed with the company name, title e.g. "Manual – Specifications for Ingredients" and date of compilation. The Authority must be notified of any change of particulars in the manuals.

Binding of manuals should be such as to allow convenient up-dating, revision, additions or removals.

1.3.5 Cross Reference between Products

There shall be no cross reference of particulars or documentation between one product and another (other than reference to above-mentioned "Manuals") except in the following circumstances:

- (i) Two or more products in the same pharmaceutical dosage form containing the same active and non active ingredients in different strengths or
- (ii) Two or more products in the same pharmaceutical dosage form containing a mixture in different strengths of the same two or more active ingredients and non active ingredients in the same proportion.

Separate application forms are required for each such product but supporting documentation if similar, may be cross-referenced provided the application for registration of these products are made at the same time, or within five years of the application for registration of the first product in the group. Appropriate reference must be clearly stated.

1.4. Submission, payment of fees and processing of applications

1.4.1 Submission of application

All applications accompanied by relevant fees, shall be addressed and submitted either in person or by courier to: *The Director General, Pharmaceutical Regulatory Authority, Plot No. 6903, Tuletaka Road, off Makishi Road, P. O. Box 3890, Lusaka, Zambia*

When an application has been received by the Director General's Office, an acknowledgement will be issued together with a reference application number for each product.

1.4.2 Payment of fees

Fees shall be paid either by bank transfer to or by certified bankers' cheque in favour of Pharmaceutical Regulatory Authority:

US Dollar Bank account

Standard Chartered Bank, Main Branch, Cairo Road, Lusaka, Zambia

US Dollar Bank Account Number: **8700211468100**

Or

Zambia Kwacha Account

Standard Chartered Bank, North-End Branch, Cairo Road, Lusaka,

Zambia

ZMK Bank Account: **0100122033800**

All bank charges shall be borne by the applicant.

1.4.3 Processing of applications

Processing of an application shall only be done on complete applications. The Authority may during evaluation of the product request for clarification or additional data or samples and the applicant is obliged to comply. Once a query has been raised, the processing shall halt until after the query has been attended. The processing of an application takes about 180 days. Immediately after the processing is completed applicants will be informed. The Authority as part of the evaluation of the product may conduct pre-registration GMP inspection to verify compliance thereof.

1.5. Registration

When a product meets the prescribed registration requirements, the applicant will be informed to that effect.

A product registration licence together with such conditions as the Authority may determine shall be issued.

1.5.1 Validity of registration

The registration of a product shall be valid for five (5) years unless sooner suspended, cancelled or revoked by the Authority or terminated by the Product licence holder. The validity of registration shall be subject to payment of prescribed annual retention fees

1.5.2 Termination of product registration

The Authority may by giving reasons in writing refuse, suspend, cancel or revoke the registration of a product, or amend the conditions of its registration.

The registration holder may by giving a 60 days written notice and reasons to the Authority terminate the registration of a registered product.

1.5.3 A duplicate of the product licence may be issued upon request accompanied by police report and on payment of a prescribed fee

1.5.4 Appeals

Any person aggrieved by a decision of the Authority in relation to any application for registration of a product may make representations to the Authority Board whereby he shall submit his representation in writing to the Authority Board within 30 days. However if after reconsideration of the representations, the Authority Board still rejects the application, the applicant may within 30 days appeal to the Minister for Health.

The appeal shall be submitted in writing giving reasons as to why the decision of the Authority should be modified or quashed. The reasons must be supported by references from peer review journals, books or official compendia. In the event that the minister upholds the decision of the Authority, the applicant shall pay a fee as determined by the Authority. The minister after receiving an appeal shall constitute an Appeals Committee comprising of a retired judge who shall be the chairman, physician or Veterinary surgeon specialized in the field for which the product is targeted, a specialist in vaccines or immunology, a clinical pharmacologist, a toxicologist, and a pharmacist specialized in pharmaceuticals or industrial pharmacy. The committee shall consider the appeal and call witnesses to testify or clarify on any issue as it may think fit. The committee, after due consideration, shall submit a report to the minister for action.

PART 2

SUMMARY OF PRODUCT CHARACTERISTICS

Provide here a complete and concise summary of product particulars as would normally appear in product monographs, package inserts, immunogenic information sheets, data sheets etc. The recommended format is given below:

2.1. Name and dosage form of product

State here the name and dosage form under which the product is/will be marketed in Zambia. International Non-proprietary Name (INN) shall be in block letters and a trade mark in small letters.

2.2. Therapeutic class

State the proposed therapeutic class of the product as in Appendix I.

2.3. Description

State briefly physical appearance of the product including colour and other relevant features e.g. cream coloured emulsion, white to off white freeze dried powder etc.

2.4. Name(s) and strength(s) of active ingredient(s) (immunogenic substance)

Give the name of the active ingredient(s) the quantitative content (strength) of each ingredient in the product. Strength shall be given per unit dosage form e.g. mg/ml, IU/g, IU/ml etc.

2.5. Mode of action

Describe briefly the main mode of action responsible for the immunological activity of the product.

2.6. Toxicology

Give a concise summary of the results of toxicity studies performed with the product, stating briefly where applicable, animal species, dosage levels, route and duration of administration and findings.

2.7. Indication

State briefly recommended clinical use(s) of the product.

2.8. Contraindications

State conditions for which or under which the product should not be used.

2.9 Reconstitution

Give detailed information on reconstitution where applicable

2.10. Dose and dosage regimen

State the dose, dosage schedule and route of administration appropriate for each therapeutic indication. (In case of veterinary Vaccines, the dosage and route of administration for each species of animal for which the product is intended to be specified)

2.11. Adverse Event Following Immunization (AEF)

State briefly the adverse events following Immunization

2.12. Immunogenic interactions

State briefly the immunological interactions if any following co-administration of vaccines or immunological substance(s)

2.13. Precaution(s)/warning(s)

State briefly precautions and warnings necessary to ensure safe and effective use of the product and, disposal of containers, expired and/or unused product.

2.14. Storage condition(s)

State briefly the recommended storage conditions (temperature, humidity, light), shelf life and any special user instruction and precautions.

2.15. Supporting documents:

Provide Batch or Lot Release Certificate and Original Certificate of a Pharmaceutical Product issued by the Drug Regulatory Authority of the country of origin.

2.16. Information leaflet.

Submit information leaflet as per format prescribed in Appendix II.

2.17. Labeling:

The product shall be labeled as in accordance to the format described in Appendix III.

Note:

- a. Five copies of package inserts, labels should be attached at the end of this section.
- b. Where a heading is not applicable or information not available, indicate clearly in the appropriate sections.

PART 3

CHEMISTRY, MANUFACTURING AND QUALITY OF ACTIVE PHARMACEUTICAL INGREDIENTS FOR VACCINES AND BIOLOGICAL PRODUCTS

3.1. Composition of the product

A list of the active ingredients (immunogens) and other additives shall be given and their amount per unit dose shall be stated.

3.1.1 Description

This section should contain a clear description of the immunogenic substance. The biological name (including strain and/or clone designation) or chemical name, including any approved name, should be provided. The description should also include the source of the cells, including microbes from which the immunogenic substance was derived, the active components of the cell fractions or purified antigens and the physical and chemical properties of the synthetic immunogenic substance. Any chemical modification or conjugation of the immunogenic substance should be described in detail. Also a list of any inactive substance which may be present in the immunogenic substance should be provided.

3.1.2 Characterization

This section should contain a description of all analytical testing performed to characterize the immunogenic substance with respect to identity, potency and stability. Test results can be presented in either tabular form, legible copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis or other appropriate formats. Data should be well organized and fully indexed to enable easy access. Results for quantitative assays should be presented as actual data not generally as "Pass" or "Fail".

3.1.3 Biological activity tests

Further characterization of vaccines may include

- 3.1.3.1 Specific identity testing
- 3.1.3.2 Cytometric analysis
- 3.1.3.3 Neurovirulence testing, if applicable
- 3.1.3.4 Serotyping
- 3.1.3.5 Electrophoretic typing
- 3.1.3.6 Inactivation studies
- 3.1.3.7 Neutralization assay and
- 3.1.3.8 Titrations
- 3.1.3.9 Pathogenicity assays if live vaccine

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 substance shall be provided.

A complete description of the protocol used for each bioassay, the control standard reference number used, the validation of the inherent variability of the test and the established acceptance limits for each assay should be included. The characteristics of specific antibodies used in the immunochemical or serological assays shall also be included.

3.2. Description of the manufacturing facility

3.2.1 Identification

The application shall include the name(s), address(es) and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the immunogenic substance.

3.2.2 Manufacture of other products

A comprehensive list of additional products that are manufactured or manipulated in the same area(s) used to produce the immunogenic substance that is the subject to this application shall be provided. This section should include a brief description of the type and development status of the additional immunogenic substances/product and indicate the areas into which these other products will be introduced, whether on an ongoing or campaign basis and what manufacturing steps will be performed in the multiple use area(s). The applicant should also indicate whether the manufacture of other products will utilize the same contact equipment and if so, how that equipment will be cleaned and validated between operations for the manufacturing of different products. Data should be provided for the validation and cleaning in the appropriate section.

3.2.3 Layout

The applicant shall submit a simple flow diagram of the general layout of the facilities which traces the immunogenic substance through the manufacturing process. The diagram(s) should be sufficiently clear to enable visualization of the production flow and to identify adjacent operations that may create particular concerns.

3.2.3 Precautions against contamination

For all areas in which operations for the preparation of cell banks and product manufacturing are performed, including areas for the handling of animals used in production, the information concerning precautions taken to prevent contamination or cross contamination shall be provided.

3.3. Method of manufacture

A detailed description of the manufacturing and controls for each immunogenic substance shall be provided to demonstrate proper quality control and prevention of possible contamination with adventitious agent(s).

3.3.1 Raw materials

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

3.3.2 Flow charts

A complete visual representation of the manufacturing process flow shall be provided for each immunogenic substance. This flow chart shall show the steps in production, equipment and materials used, area where the operation is performed and a complete list of the in-process controls and tests performed on

the product at each step. In-process holding steps should be included with time and temperature limits indicated.

3.4. Detailed description of source of raw material(s)

The following minimum information shall be provided

3.4.1 Animal sources

- a. The species and age of animals
- b. The health status of the animals e.g. specific pathogen free
- c. The results of adventitious agent
- d. The animal husbandry practices e.g. quarantine procedures used to ensure the suitability of the animals.
- e. The veterinary and laboratory monitoring used to ensure the suitability of the animals.
- f. A description of the inoculation of the animals and
- g. A description and the method of harvest.

3.4.2 Virus sources

- a. The original source of the virus
- b. The passage history of the virus strains
- c. Details of the seed lot system
- d. The culture techniques for virus seed maintenance.

3.4.3 Microbial Cellular sources

- a. Microbial cells
- b. Origin of isolate
- c. Species
- d. Biochemistry (fermentation profile etc.)
- e. Strain identifier and specific identifying characteristics (serotype etc)
- f. Virulence (attenuation method, if performed)
- g. Generic characterization, if known markers, inserts, deletions, etc.)
- h. Plasmids and
- i. Genetic stability

3.4.4 Animal cells

(i) Primary cells

- a. The species and age of the animals and source of tissue from which the cells are derived
- b. The health status of the animals from which the cells are derived e.g. specific pathogen free
- c. The animal husbandry practices (quarantine etc.) used to ensure the suitability of the animals
- d. The veterinary and laboratory monitoring used to ensure the suitability of the animals
- e. A description of the preparation of primary cell substrates and
- f. An explanation of the concurrent testing done to demonstrate the absence of adventitious agents and the results of those tests

(ii) Cell lines

For human cell substrates the source of cells shall be clearly described including the materials and methods used the tissue or organ of origin

ethnic and geographical origin, age, gender and general physiological condition. The health or media history of the donor, if known shall be provided along with the results of any tests for pathogenic agents. For animal cell lines, relevant description of the source may include species, strains, breeding conditions, tissue or organ of origin, geographical origin, age, sex and general physiological condition of the original donor. Testing for detection of adventitious agents should be undertaken with consideration of the possible agents

3.4.5 DNA Recombinant Products

3.4.5.1 Genetic constructs and recombinant cell lines

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

a. Host cells

A description of the source, relevant phenotype, and genotype shall be provided for the host cell used to construct the biological production system. The results of the characterization of the host cell for phenotypic and genotypic markers including those that will be monitored for cell stability, purity and selection shall be included.

b. Gene construct

A detailed description of the gene, which was introduced into, the host cells, including both the cell type and origin of the source material shall be provided. A description of the method(s) used to prepare the gene construct and a restriction enzyme digestion map of the construct shall be included. The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence shall be provided including annotation designating all important sequence features.

c. Vector

Detailed information regarding the vector and genetic elements shall be provided, including description of the source and function of the component parts of the vector e.g. origins of replication, antibiotic resistance genes, promoters, enhancers. A restriction enzyme digestion map indicating at least those sites used in construction of the vector shall be provided. Genetic markers critical for the characterization of the production cells shall also be indicated

d. Final gene construct

A detailed description shall be provided of the cloning process which resulted in the final recombinant gene construct. The information shall include a step-by-step description of the assembly of the gene fragments and vector or other genetic elements to form the final gene construct. A restriction enzyme digestion map indicating at least those

sites used in constructions of the final product construct shall be provided.

e. **Cloning and establishment of the recombinant cell lines**

Depending on the methods to be utilized to transfer a final gene construct or isolated gene fragments into its host, the mechanism of transfer, copy number, and the physical state of the final construct inside the host cell (i.e. integrated or extra chromosomal) shall be provided. In addition, the amplification of the gene construct, if applicable, selection of the recombinant cell clone and establishment of the seed shall be completely described.

3.4.6 Cell Bank System

A description of the cell banking procedures used shall be provided including:

- a. The banking system used
- b. The size of the cell banks
- c. The container and closure system used
- d. A detailed description of the methods, reagents and media used for preparation of the cell banks
- e. The conditions employed for cryopreservation and storage
- f. In-process control(s) and
- g. Storage conditions. A description shall be provided for the procedures used to avoid microbial contamination and cross-contamination by other cell types present in the facility, and the procedures that allow the banked cells to be traced.

3.4.7 Master Cell Bank (MCB)

A complete history and characterization of the Master Cell Bank (MCB) shall be provided, including, as appropriate for the given cells:

- a. The biological or chemical method used to derive the cell bank
- b. Biochemistry (cell surface markers, isoenzyme analysis, specific protein or mRNA, etc.)
- c. Specific identifying characteristics (morphology, serotype etc.)
- d. Karyology and tumorigenicity
- e. Virulence markers
- f. Genetic markers
- g. Purity of culture and
- h. Media and components (e.g. serum)
- i. Any reagents added into the cell bank

3.4.8 Working Cell Bank (WCB)

This section shall also 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 cataloging of the WCB. The assays used for qualification and characterization of each new WCB shall 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 shall be supplied.

3.4.9 End of Production Cells (EPC)

For r-DNA derived immunogenic substances, a detailed description of the characterization of the EPC that demonstrates that the biological production system is consistent during growth shall be provided. The results of the analysis of the EPC for phenotypic or genotypic markers to confirm identity and purity shall 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 shall be submitted.

Detailed information on the characterization and testing of banked cell substrates shall be submitted. This shall include the results of testing to confirm the identity, purity and suitability of the cell substrate for manufacturing use.

3.4.10 Cell Growth and Harvesting

This section shall contain a description of each of the following manufacturing processes, as appropriate. The description should contain sufficient detail to support the consistency of manufacture of the immunogenic substance.

a. Propagation

This section shall contain description of:

- Each step in propagation from retrieval of the WCB to culture harvest (stages of growth)
- The media used at each step (including water quality) with details of their preparation and sterilization
- The inoculation and growth of initial and sub-cultures, including volumes, time and temperatures of incubation(s)
- How transfers are performed
- Precautions taken to control contamination
- In-process testing which determines inoculation of the main culture system
- In-process testing to ensure freedom from adventitious agents, including tests on culture cells, if applicable.
- The nature and composition of the main culture system including operating conditions and control parameters (e.g. temperature of incubation, static vs. agitated, aerobic vs. anaerobic, culture vessels vs. fermenter, volume of fermenter or number and volume of culture vessels)
- The parallel control cell cultures, if applicable, including number and volume of culture vessels
- Induction of antigen, if applicable and

- The use of antibiotics in the medium and rationale, if applicable.

b. Harvest

A description of the method(s) used for separation of crude substance from the propagation system (precipitation, centrifugation, filtration etc.) shall be provided. Brief description shall be given for the following:

- The process parameters monitored
- The criteria for harvesting
- The determination of yields and
- The criteria for pooling more than one harvest, if applicable.
- A description of the procedures used to monitor bioburden (including acceptance limits) or sterility shall be included. If the harvested crude immunogenic substance is held prior to further processing, a description of storage conditions and time limits shall be provided.

3.4.11 Purification and Downstream Processing

This section shall contain a description of the methods and materials by which intermediate forms and the final bulk of the immunogenic substance are separated and concentrated from the cells, media, solvents or solutions used in the production process. The description of each step of the purification process shall also include the accompanying analytical tests developed or adopted by the manufacturer to show identity, purity and concentration and the levels of product related and non-product related impurities.

Description shall be provided for:

(i) Inactivation (if appropriate)

- a. How culture purity is verified before inactivation
- b. The method(s) and agent(s) used for inactivation
- c. The method(s) undertaken to prevent aggregation and assure homogeneous access of inactivating agent(s)
- d. The stage in production where inactivation or killing is performed, and
- e. The parameters which are monitored
Verification of the adequacy and margin of safety achieved by the method of inactivation or killing should be provided.

(ii) Purification (if appropriate)

- a. The methods used, including specialized equipment such as columns; ultracentrifugation, ultrafiltration, and custom reagents such as monoclonal antibodies
- b. The process parameters monitored
- c. The determination of yields

- d. In-process testing (e.g. sensitivity and specificity of ELISA)
- e. The criteria for pooling more than one batch, if applicable.
- f. Sterility or bioburden monitoring and the precautions taken to prevent contamination during purification
- g. The reuse and/or regeneration of columns and adsorbents and
- h. Monitoring for residual impurities and leachable reagents.

A list of in-process controls and tests for purity, identity, and biological activity shall be provided. A list of the final acceptance criteria for the purified immunogenic substance shall be provided. If the purified substance is held prior to further processing, a description of the storage conditions and time limits shall be included.

(iii) Stability processing

A description shall be provided for any post-purification steps performed to produce a stabilized intermediate (e.g. adsorption, addition of stabilizers, addition of preservatives, lyophilization (in bulk), desiccation), and the objectives and rationale for performing each process. A description of precautions taken to monitor bioburden and prevent contamination during these processes shall also be given. If the stabilized intermediate is held prior to further processing, a description of storage conditions and time limits should be included. Verification of the stability of the immunogenic substance under the conditions described shall be provided (Process Validation).

(iv) Detoxification

For toxoid or toxoid-containing vaccines, the detoxification procedures should be described in detail for the toxin component(s):

- a. The method(s) and agent(s) used for detoxification
- b. The stage in production where detoxification is performed and
- c. The parameters which are monitored.
- d. Confirmation of detoxification.

3.4.12 Synthetic Immunogenic Substance

For the purposes of this guidance, synthetic immunogenic substance includes; linear or complex synthetic peptides, or modified synthetic or semi-synthetic immunogens such as lipopeptides to carrier protein or polysaccharide to carrier protein conjugates.

(i) Synthetic Peptides

The detail of the peptide synthesis including purification procedures shall be provided.

(ii) Conjugates and Modified Immunogenic Substance

This section of the guidance refers to immunogenic substances derived from another immunogenic substance or intermediate through chemical or enzymatic modification, e.g. conjugation of an immunogen to a carrier molecule, enzymatic or chemical cleavage and purification of the non-toxic subunit of a toxin, or derivatization. The modification may change the fundamental immunogenicity, toxicity, stability or pharmacokinetics of the source immunogenic substance. The derived immunogenic substance may include linking moieties and new antigenic epitopes.

(iii) Manufacturing procedure

This section should provide a detailed description of:

- a. The specifications and acceptance criteria, for the native immunogenic substance starting materials, which assure suitability for conjugation or modification;
- b. The conditions of all reactions and/or syntheses used to produce a semi-synthetic conjugated molecule, derivatized molecule, or subunit, including intermediate forms of the reactants and immunogenic substance; also include the process parameters which are monitored, in-process controls, testing for identity and biologic activity, and any post-purification steps performed to produce a stabilized derived immunogenic substance.
- c. Description of the methods and equipment used for separation of unreacted materials and reagents from the conjugate, derivative, or subunit, and a rationale for the choice of methods.

(iv) Specification

Specifications should be provided for each modified immunogenic substance, including identity, purity, potency, physical-chemical measurements, and measures of stability. If test results for the derived substance will be reported for final release of the immunogenic product a validation report, to include estimates of variability and upper and lower limits, should be provided for each specification. Specifications should include the amount of unreacted starting materials and process reagents unless their removal has been validated.

3.4.13 Batch Records

A completed (executed) representative batch record of the process of production of the immunogenic substance shall be provided.

3.5. Process Controls

3.5.1 In-process controls

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

3.5.2 Process Validation

A summary report, including protocols and results shall be provided for the validation studies of each critical process or factor that affects immunogenic substance specifications. The validation study reports with statistical rigor shall document the variability in each process as it relates to final specifications and quality.

(i) Propagation

A growth curve or tabular representation of growth characteristics for each propagation step, based on historical performance under specified conditions, shall be provided. Data shall be included which demonstrate the point of efficiency of induction of antigen production, if applicable. Data shall also be provided showing the stability of genetic markers under the conditions of propagation, if applicable.

ii) Harvest

For each method or combination of methods, a tabulation shall be provided of yields purity, and viability (if applicable) of the crude harvest, based on historical performance.

(iii) Inactivation

Inactivation or killing curves, or a tabular representation, based on historical performance shall be provided. Validation of the titration method to measure residual live agents, including sensitivity in a background of inactivated agents, shall be provided.

(iv) Purification

For each method or combination of methods used, a tabulation of yields, purity and biological activity shall be provided. Verification of the removal or dilution of product related and non-product related impurities, e.g. processing reagents, endotoxin contaminating cell proteins or nucleic acids, and other residual contaminants shall be included. A standard denominator (e.g. international units) shall be used to facilitate comparison through processing, concentration, or dilution.

(v) Microbiology

A description and documentation of the validation studies for any processes used for media sterilization, effectiveness of preservatives, decontamination, inactivating cells prior to their release to the environment, if such inactivation is required, etc.

shall be provided. If the immunogenic substance is intended to be sterile, information shall be submitted.

(vi) Control of Bioburden

For each process which is not intended to be sterile, documentation of the control of extraneous bioburden by a tabulation of in-process testing for bioburden shall be provided.

3.6. Manufacturing Consistency

Consistency of the manufacturing process for each vaccine component shall be demonstrated by manufacturing at least three, preferably consecutive, batches of immunogenic substance of a size corresponding to that for routine production. The establishment and use of reference standards in assuring consistency in product characteristics shall be described.

3.6.1 Reference Standards

A description of the preparation, characterization, and stability of primary and working reference standards shall be provided. A detailed description of the procedures to qualify new lots of reference standards and acceptance criteria for a new reference standard shall be included.

3.6.2 Release Testing

Release (acceptance criteria) testing results and other (for information only) characterization data (e.g. certificates of analysis) for each batch shall be submitted.

3.7. Immunogenic Substance Specifications

3.7.1 Specifications

This section shall contain the specifications and tests for each immunogenic substance. These shall include assays for identity, purity, potency (biologic effect), physicochemical measurements which predict potency, and where applicable, measures of stability. For highly purified substances, purity in reference to the theoretical composition shall be presented. In some cases test results for the stabilized intermediates of component antigens shall be included in the final release of the immunogenic product. The results of the validation studies for each of these specifications, including estimates of variability and upper and lower limits shall be provided.

3.7.2 Impurities Profile

This section should include a discussion of the impurities in the immunogenic substance. The identity and quantity of impurities shall be provided along with the analytical data (gels, elution profiles, Western blots etc.) which support the impurities profile. Impurities that shall be characterized and quantitated include:

- Product related impurities (variants or alterations of antigen occurring during processing or storage)
- Process related impurities
- Media components
- Cell substrate proteins or nucleic acids or

- Process reagents which have not been removed by the purification process

3.8. Reprocessing

This section shall include detailed information on any reprocessing that may be done on each immunogenic substance.

3.8.1 The information provided for each reprocessing procedure shall include:

- i. A description of the conditions or criteria, determined from process controls or specifications, which indicate the need for re-processing
- ii. A description of the reprocessing step
- iii. The Standard Operating Procedure for the step
- iv. A description of any additional or modified in-process controls or specifications which are included to monitor re-processing steps
- v. A description of the modifications in batch numbers and documentation of re-processing in the Batch Production Record (BPR) and
- vi. The evidence derived from validation studies which assure that product identity, purity, potency and stability is preserved for re-processed batches.

3.9. Container and Closure System

A description of the container and closure system, and its compatibility with the immunogenic substance shall be submitted. The submission shall include detailed information concerning the supplier, address and the results of compatibility, toxicity and biological tests. If the immunogenic substance is intended to be sterile, evidence of container and closure integrity for the duration of the proposed expiry period shall be provided. Sterility procedures on the container shall also be provided.

3.10. Immunogenic Substance Stability

This section shall contain information on the stability of the immunogenic substance and any in-process material at each holding step.

PART 4

CHEMISTRY, MANUFACTURING AND QUALITY OF FINISHED VACCINE/ BIOLOGICAL MEDICINAL PRODUCT

This section should contain information on the final Biological medicinal product including all immunogenic substances and excipients in the final 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. For all ingredients of human or animal origin, testing results or certificates of analysis demonstrating their freedom from adventitious agents should be provided.

4.1. Composition

A list should be provided of all components in the medicinal product, including immunogenic substance(s) and other ingredients, with their units specifications and batch quantities. The reason for inclusion of ingredients in the formulation shall be stated.

4.2. Analytical methods for medicinal product ingredients

This section should contain a description of tests for all ingredients, if not specified in the immunogenic substance section.

4.2.1 Description

A qualitative statement describing the physical state (lyophilized solid, powder, liquid) and colour and clarity of the medicinal product and other ingredients should be provided

4.2.2 Identity

The method used to establish the identity of the medicinal product should be described. The description should include an evaluation of its specificity and sensitivity

4.2.3 Purity and impurities

This section shall include information on the purity of the final product including identification and quantitation of impurities, degradation products inherent in the final dosage form. If impurities are known to be introduced or formed during the production of the immunogenic product, the acceptable limits of these impurities shall be determined and included in the specifications.

4.2.4 Potency

A description shall be provided of the potency assay for the medicinal product. Information shall be submitted on the sensitivity, specificity, and variability of the assay including the data from the material used to prepare clinical/pre-clinical lots which were used to set the acceptance limits for the assay.

4.3. Manufacturer and Facilities

The name(s) and address (es) of all manufacturers involved in the manufacture and testing of the Biological medicinal product including contractors, and a description of the responsibility (ies) of each should be submitted.

4.4. Manufacturing Methods

This section shall include a detailed description of the manufacturing process flow of the formulated bulk and finished medicinal product including the sterilization operations, aseptic processing procedures, lyophilization, and packaging. Accompanying this narrative, a flow chart shall be provided that indicates the production steps, the equipment and material used and a listing of the in-process controls and tests performed on the product at each step. A Master Production Record (MPR) for the medicinal product shall be provided, including complete manufacturing instructions for adsorption (if applicable), formulation, filling, labelling and packaging. Results of studies validating the compatibility of the components including the adjuvants and/or preservatives, if applicable, should be provided. Lot-to-lot consistency of the immunogenic product shall be demonstrated.

4.5. Medicinal Product Specifications

4.5.1 Sampling procedures

The sampling procedures for monitoring a batch of finished medicinal product shall be included.

4.5.2 Specifications and methods

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 product and the specifications used for the immunogenic product shall be submitted. Certificates of analysis and analytical results for at least five consecutive batches shall be provided.

4.5.3 Validation results

The results of studies validating 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 validation. For analytical methods in compendia sources, the appropriate citations shall be provided.

4.6. Container and closure system

A description of the container and closure system, and its compatibility with the medicinal product shall be submitted. Detailed information concerning the supplier(s), address(es), and the results of compatibility, toxicity and biological tests shall be included. For sterile product, evidence of container and closure integrity shall be provided for the duration of the proposed expiry period. Sterility procedures on the container shall also be provided.

4.7. Microbiology

Information for microbial tests shall be submitted.

4.8. Lyophilization

A validation summary for lyophilization of the Biological medicinal product shall be given which includes:

- i. A narrative description of the validation (or protocol)
- ii. Certification that Installation Qualification (IQ) and Operational Qualification (OQ) have been completed
- iii. A validation data summary
- iv. Explanation of all excursions or failures and
- v. Deviation reports and results of investigations of all excursions or failures.

4.9. Stability of the product

Evidence shall be provided to demonstrate that the product is stable for the proposed validity period under the indicated storage conditions.

Stability data submitted should be for at least three consecutive batches.

Generally the study shall be conducted and documented in the following way:

4.9.1 Protocol

A detailed protocol for the assessment of the stability of immunogenic product in support of the proposed storage condition and expiration dating periods shall be provided. The protocol should include all necessary information which demonstrates the stability of the product throughout the proposed expiration dating period, including well defined specifications and test intervals.

4.9.2 Stability program

A plan for an on-going stability program shall be provided. This shall 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.

4.9.3 Data in support of stability of the product shall include:

- (i) Container under which the study was done
- (ii) Batch number
- (iii) The type of study i.e. real time, accelerated
- (iv) A detailed protocol
- (v) Manufacturing and expiry date of the batches subjected to stability testing
- (vi) Summarised results including:
 - a. Proposed storage condition
 - b. Proposed shelf life
 - c. In-use storage condition and shelf life
 - d. Parameters tested
 - e. Frequency of testing

PART 5
PRE CLINICAL TOXICOLOGICAL DATA

5.1. Toxicology

Particulars of laboratory tests and their conclusions performed to demonstrate all aspects of toxicity of the product to predict toxic effects during use and environmental impact with special reference to:

- i. Single dose toxicity
- ii. Repeat dose toxicity
- iii. Genotoxicity including mutagenicity
- iv. Carcinogenicity
- v. Reproductive toxicity
 - a. Effects on fertility and early embryonic development
 - b. Effects on embryonic-foetal development
 - c. Effects on prenatal and postnatal development
- vi. Local tolerance (potential for adverse effects at site of administration)
- vii. Reversion of virulence studies for live attenuated vaccines to investigate the possibility of the vaccine reverting into its wild, disease causing form (also called back passage studies)
- viii. Studies to prove inactivation of killed organism vaccines

5.2. Effect of the biological medicinal product on the ecosystem

Provide brief information of the effect of the product on the ecosystem.

5.3. Pharmacology

Particulars of laboratory tests and their conclusions performed to demonstrate all aspects of pharmacology of the product, and to predict mode of action, with special reference to:

- i. **Pharmacodynamic studies (in laboratory animals or humans)**
 - a. Primary pharmacodynamics – primary action in target system.
 - b. Secondary pharmacodynamics – resultant action in target systems
 - c. Safety pharmacology – pharmacodynamics in non target systems leading to side effects
 - d. Pharmacodynamic immunogenic interactions
- ii. **Pharmacokinetics studies (in laboratory animals and/or humans)**
 - a. Absorption, distribution, metabolism, excretion characteristics
 - b. Relationships between pharmacokinetic characteristics and
 - c. therapeutic and toxic effects
 - d. Pharmacokinetic immunogenic interactions observed or predicted.

Note: Each study shall include the following;

- Objective
- Experimental protocol including methodology and materials
- Summarised results and their statistical analysis
- Discussion and conclusions

5.4. Particulars of side effects, contra-indications, etc. of the immunogenic

The adverse effects of the product, conditions in which it should not be used, precautions before or during use shall be stated.

5.5. Bibliography

Reference to literature shall be precise, quoting the author, year of publication and the relevant page(s). Photocopies of relevant literature may be attached.

PART 6

CLINICAL SAFETY AND EFFICACY DATA

Particulars of tests which have been performed in human beings (human vaccines) or target animals (Veterinary vaccines) regarding the efficacy of the efficacy of the immunogenic and the indications for which it will be used (clinical trials). Details of studies on the following subjects shall be provided:

6.1. Immunogenicity, efficacy and safety studies (in target species) including:

- i. Controlled clinical trials on efficacy (vaccination-challenge studies, field efficacy studies)
- ii. Studies on potential beneficial interactions (boosting) with other vaccines of the same type
- iii. Studies on potential decrease in efficacy when administered at the same time as other vaccine (interference)
- iv. Studies on interchangeability with other vaccines of the same type
- v. Local and systemic tolerance studies to determine the maximum tolerable dose
- vi. Field safety studies
- vii. Studies on Drug/Vaccine interaction

6.2. Individual clinical studies protocol shall include the following

- i. Objectives
 - ii. Identity and qualifications of key personnel involved
 - iii. Location(s) of study
 - iv. Dates of study
 - v. Design
 - a. Selection of subjects (inclusion, exclusion criteria)
 - b. Selection of controls
 - c. Selection of control treatment (if applicable)
 - d. Number of subjects
 - e. Response variables – end points
 - f. Minimisation of bias – randomisation, blinding, compliance
- vi. Treatments given – identity and quality of the investigational and control products used, dosage used, duration of treatment, duration of observation periods, any concurrent treatments and their justification
 - vii. Analytical methods for determining immunogenic concentrations in body fluids, tissues
 - viii. Analysis of results including statistical analysis
 - ix. Discussions and conclusions on efficacy and safety.

6.3. Particulars of therapeutic effects and indications of product

The proposed therapeutic use(s) of the product shall be stated. Evidence of potential benefit suitability of use in Zambia shall be provided.

6.4. Bibliography

Reference to literature shall be precise, quoting the author, year of publication and the relevant page(s). Photocopies of relevant literature may be attached.

APPENDIX I

ANATOMICAL CHEMICAL CLASSIFICATION SYSTEM OF BIOLOGICALS INCLUDING VACCINES AND OTHER IMMUNOLOGICAL PRODUCTS

The Anatomical Therapeutic Chemical system serves as a basis for classifying immunogenics according to two numerical and ending with an alphabet:

J BIOLOGICALS INCLUDING VACCINES AND OTHER IMMUNOLOGICAL PRODUCTS FOR HUMAN USE

J06A IMMUNE SERA AND IMMUNOGLOBULINS
J06B IMMUNE SERA
J06C IMMUNOGLOBULINS
J07A BACTERIAL VACCINES
J07B DNA VACCINES
J07C VIRAL VACCINES
J07D BACTERIAL AND VIRAL VACCINES COMBINED
J07X OTHER VACCINES

J ANTIINFECTIVES FOR SYSTEMIC USE

J06 IMMUNE SERA AND IMMUNOGLOBULINS

J06B IMMUNOGLOBULINS

J06BB Specific immunoglobulins

J07 VACCINES

J07A BACTERIAL VACCINES

J07AC Anthrax vaccines

J07AD Brucellosis vaccines

J07AE Cholera vaccines

J07AF Diphtheria vaccines

J07AG Hemophilus influenzae B vaccines

J07AH Meningococcal vaccines

J07AJ Pertussis vaccines

J07AK Plague vaccines

J07AL Pneumococcal vaccines

J07AM Tetanus vaccines

J07AN Tuberculosis vaccines

J07AP Typhoid vaccines

J07AR Typhus (exanthematicus) vaccines

J07AX Other bacterial vaccines

J07B VIRAL VACCINES

J07BA Encephalitis vaccines

J07BB Influenza vaccines
J07BC Hepatitis vaccines
J07BD Measles vaccines
J07BE Mumps vaccines
J07BF Poliomyelitis vaccines
J07BG Rabies vaccines
J07BH Rota virus diarrhea vaccines
J07BJ Rubella vaccines
J07BK Varicella zoster vaccines
J07BL Yellow fever vaccines
J07BM Papillomavirus vaccines
J07BX Other viral vaccines

J07CA Bacterial and viral vaccines, combined

J07CA01 Diphtheria-poliomyelitis-tetanus
J07CA02 Diphtheria-pertussis-poliomyelitis-tetanus
J07CA03 Diphtheria-rubella-tetanus
J07CA04 Hemophilus influenzae B and poliomyelitis
J07CA05 Diphtheria-hepatitis B-pertussis-tetanus
J07CA06 Diphtheria-Hemophilus influenzae B-pertussis-poliomyelitis-tetanus
J07CA07 Diphtheria-hepatitis B-tetanus
J07CA08 Hemophilus influenzae B and hepatitis B
J07CA09 Diphtheria-Hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B
J07CA10 Typhoid-hepatitis A
J07CA11 Diphtheria-Hemophilus influenzae B-pertussis-tetanus-hepatitis B
J07CA12 Diphtheria-pertussis-poliomyelitis-tetanus-hepatitis B
J07CA13 Diphtheria-hemophilus influenzae B-pertussis-tetanus-hepatitis B-meningococcus A + C

J07X [OTHER VACCINES](#)

QI BIOLOGICALS INCLUDING VACCINES AND OTHER IMMUNOLOGICAL
PRODUCTS FOR VETERINARY USE

QI01 IMMUNOLOGICALS FOR AVES

- A Domestic fowl
- B Duck
- C Turkey
- D Goose
- E Pigeon
- F Pheasant
- G Quail
- H Partridge
- I Ostrich
- K Pet birds
- X Aves, others

QI02 IMMUNOLOGICALS FOR BOVIDAE

- A Bovine/Cattle
- B Buffalo
- X Bovidae, others

QI03 IMMUNOLOGICALS FOR CAPRIDAE

- A Caprine/Goat
- X Capridae, others

QI04 IMMUNOLOGICALS FOR OVIDAE

- A Ovine/Sheep
- X Ovidae, others

QI05 IMMUNOLOGICALS FOR EQUIDAE

- A Equine/Horse
- B Azinine/Donkey
- C Hybride
- X Equidae, others

QI06 IMMUNOLOGICALS FOR FELIDAE

- A Feline/Cat
- X Felidae, others

QI07 IMMUNOLOGICALS FOR CANIDAE

- A Canine/Dog
- B Fox
- X Canidae, others

QI08 IMMUNOLOGICALS FOR LEPORIDAE

- A Rabbit
- B Hare
- X Leporidae, others

QI09 IMMUNOLOGICALS FOR SUIDAE

- A Porcine/Pig
- X Suidae, others

QI10 IMMUNOLOGICALS FOR PISCES

- A Atlantic salmon
- B Rainbow trout
- C Carp
- D Turbot
- E Ornamental fish
- X Pisces, others

QI11 IMMUNOLOGICALS FOR RODENTS

A Rat
B Mouse
C Guinea-pig
X Rodents, others
QI12 IMMUNOLOGICALS, OTHER SPACIES
A Red deer
B Reindeer
C Mink
D Ferret
E Snake
F Bee
X Others

APPENDIX II

Package insert information requirements

Each package of a product shall be accompanied by a package insert either as a separate entity or as an integral part of the package on which shall be printed in readable letters in English language under the headings and in the format specified below:

- (a) Name (both proprietary and international non-proprietary names) and dosage form of the product
- (b) Identification (description of the product and package)
- (c) Content and quantity of active ingredients and non active ingredients in a dosage unit or suitable mass or volume or unit of the product.
- (d) Therapeutic class
- (e) Indications
- (f) Contraindications
- (g) Side effects (adverse drug reactions) and drug interactions
- (h) Precautions and warnings
- (i) Dosage regimen and directions for use
- (j) Symptoms and treatment of overdose
- (k) Presentation (packing and pack size)
- (l) Storage instructions and shelf life
- (m) Name and address of product licence holder
- (n) Name and address of manufacturer and country of origin
- (o) Date of publication of the insert

APPENDIX III

Labeling requirements

Every immediate container of any medicine shall be affixed with a label bearing the following particulars pertaining to the contents of such container in clearly legible indelible letters in English language:

- (a) International Non- proprietary (in bold letters) and proprietary Name (in non bold letters)
- (b) Registration number in Zambia (once is approved for registration)
- (c) The dosage form of the medicine
- (d) Storage instructions and shelf life
- (e) The content of the medicine in the container expressed in the appropriate unit or volume of the medicine.
- (f) Name and address of product licence holder
- (g) In case of contract manufacturing, the name and address of manufacturer printed in the same letter size as those of the product licence holder as follows: *“Manufactured for.....(name and address of product licence holder) by.....(name and address of manufacturer)”*. In this case (f) shall not be applicable.
- (h) Distribution category – “The words Prescription Only Medicines” or “General sales medicines” or “Pharmacy medicines” whichever the case may be
- (i) Where applicable the instruction:
 - “Shake well before use”
 - “For external use only”
 - “Keep out of reach of children”
 - “For animal treatment only” or for veterinary use only”
- (j) Where applicable, indications and recommended dosage of the medicine.
- (k) In case of medicines for injection, route of administration by suitable words or abbreviations such as IM, IV etc.
- (l) The batch or lot number of the medicine
- (m) The manufacturing and expiry date of the medicine

In case the medicine’s package bears both the immediate container label and outer container label, the above requirements shall apply to the outer container label as well.

Appendix IV

APPENDIX 4- REGULATION FORM

PRA FN -----

Pharmaceutical Regulatory Authority
APPLICATION FORM
For registration of Biologicals in Zambia

For Official use only	
Application No.	Date

1. Proprietary name :
1.1 Name of the active ingredient(s)
1.2 Pharmacotherapeutic classification (Anatomic-Therapeutic and chemical system)
2. Dosage form
2.1 Route of administration

2.2 Container, closure and administration devices :

2.3 Pack size(s) :

2.4 Recommended shelf life (in months) :

2.5 Recommended shelf life (for multi-dose after first opening of container)

2.6 Recommended shelf life (after reconstitution)

2.7 Storage conditions:

2.8 Special user instructions and pre-cautions (where applicable).:

3. Proposed indications of the product :

4. Complete composition per dosage unit

Name (inn) of Ingredients	Specifications	Quantity	Unit of measure	Reason for inclusion
(I)				
(II)				
(III)				
(IV)				
(V)				
(VI)				
(VII)				

5. Details of applicant

Name:

Business Address:

Postal Address:

Country:

Phone No:

Fax:

E - mail:

5.1 Details of a resident responsible agent/distributor (who must be nominated by the applicant and submit evidence of power of attorney)

Name:

Business Address:

Postal Address:

Phone:

Fax:

E - mail:

6. Details of manufactures(s) involved in production activities of the product.

NAME OF COMPANY	ACTIVITY (e.g. Production of master seed)	SITE (Business Address, Phone and Country)
(i)		
(ii)		
(iii)		
(iv)		

7. Status of marketing authorization/registration in the country of origin (if approved provide registration number) :

8. Registration status in the SADC member states and in other countries

Registered: Country of origin:

Date of authorization:

Authorization number:

Trade name:

Pending: Country:

Date of submission:

Trade name:

Rejected: Country:

Date of rejection:

Reason for rejection:

Trade name:

Withdrawn (by applicant before registration) Country:

Date of withdrawal:

Reason for withdrawal:

Trade name:

Withdrawn (by applicant after registration) Country:

Date of withdrawal:

Reason for withdrawal:

Trade name:

Suspended/Revoked Country:

(By Regulatory Authority) Date of suspension/

Revocation

Reason for Revocation

Trade name:

9. Declaration by an applicant

I, the undersigned certify that all the information in this form and all accompanying documentation is correct. I further certify that I have examined the following statements and I attest to their correctness:

- 9.1. The current edition of the WHO guideline on “**Good Manufacturing Practice** and/or equivalent national guideline, is applied in full in all premises involved in the manufacture of this product.
- 9.2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record.
- 9.3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.
- 9.4. Each batch of all starting materials is either tested or certified (in accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications before it is released for manufacturing purposes.
- 9.5. All batches of the active ingredient(s) (raw materials are obtained from the source(s) specified in the accompanying documents.
- 9.6. No batch of active ingredient will be used unless a copy of the batch certificate established by the manufacturer of that active ingredient is available.
- 9.7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for the manufacturing purposes.
8. Each batch of the finished product is either tested, or certified against the full specifications in the accompanying documentation and complies fully with release specifications before it is released for sale.
9. The person releasing the product be an authorized person as defined by the WHO guideline.
10. The analytical procedures for control of the finished product have been validated
11. All the documents referred to in this application are available for review during a GMP inspection.
12. Clinical Trials were conducted in accordance with Good Clinical Practice (GCP).

I also agree that:

1. The holder of marketing authorization/registration certificate is obliged to follow Zambian requirements for handling adverse reactions of the product.
2. The holder of registration certificate is obliged to follow Zambian requirements for handling batch recalls.

Name:

Qualification:

Position in the company:

Signature:

Date: Official stamp:

Appendix V

SI No 7 of 2008 on fees and charges

PRODUCT REGISTRATION AND RETENTION

NO:	<u>DESCRIPTION</u>	FEE UNITS (1 fee Unit = K180)	REGISTRATION FEES (ZMK)	FEE UNITS (1 fee Unit = K180)	RETENTION FEE (ZMK)
1.	<u>Human medicines</u> Application for registration				
	(i) Imported as finished product	21,112	3,800,000.00	14,056	2,530,000.00
		18,334	3,300,000.00	14,056	2,530,000.00
	(ii) Packaged in Zambia	4,223	760,000.00	2,778	500,000.00
	(iii) Locally manufactured	23,334	4,200,000.00	11,278	2,030,000.00
	(iv) New Chemical Entities	23,334	4,200,000.00	11,278	2,030,000.00
	(v) Biological products including vaccines				
2.	<u>Veterinary medicines</u> Application for registration:	12,778	2,300,000.00	10,556	1,900,000.00
	(i) Imported as a finished product	8,445	1,520,000.00	10,556	1,900,000.00
		2,834	510,000.00	2,223	400,000.00
	(ii) Packaged in Zambia				
3.	(iii) Locally manufactured				
	<u>Herbal medicinal product</u> Application for registration:	21,112	3,800,000.00	14,056	2,530,000.00
	(i) Imported as a finished product	12,778	2,300,000.00	10,556	1,900,000.00
	(ii) Herbal medicinal product packaged in Zambia	4,223	760,000.00	2,778	500,000.00
	(iii) Herbal medicine locally Manufactured				
4.	<u>Allied substances</u> (ii) Registration of an allied substance	4,223	760,000.00	2,778	500,000.00

