AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

African Medicines Regulatory Harmonisation (AMRH)

Evaluation of Medicinal Products Technical Committee (EMP-TC)

APPLICANT'S HANDBOOK

Guidelines for Human Biotherapeutic Products

EMP-TC/AGBT/V001

Table of Contents

Abbreviations and Acronyms

BMRs - Batch Manufacturing Records
CMC - Chemistry, Manufacturing and Controls
CA - Clinical Assessor
DNA - Deoxyribonucleic Acid
DP - Drug Product
DS - Drug Substance
EAC - East African Community
EMA - European Medicines Agency
EMP TC - Evaluation of Medicinal Products Technical Committee
EU - European Union
GCP - Good Clinical Practice
GLP - Good Laboratory Practice
GMP - Good Manufacturing Practice
ICH - International Council for Harmonization
INN - International Non-proprietary Name
MOA - Mechanism of Action
NCE - New Chemical Entity
NMRA - National Medicines Regulatory
Ph. Eur - European Pharmacopeia
PK/PD - Pharmacokinetic/Pharmacodynamic
PBRER - *Periodic Benefit-Risk Evaluation Report*
RMP - Risk Management Plan
WHO - World Health Organization

Introduction

These guidelines prescribe data required to be submitted to the EMP TC to demonstrate the safety, efficacy and quality of biotherapeutic protein products prepared by recombinant Deoxyribonucleic Acid (DNA) technology, (rDNA-derived biotherapeutics) and intended for use in human.

These guidelines have been developed based on the scientific guidelines and recommendations for quality, efficacy and safety adopted from WHO TRS 987, Annex 4. Some aspects of manufacturing and quality control in these guidelines may apply to protein-based vaccine antigens made by rDNA technology. However, more detailed guidelines and recommendations on vaccine evaluation in terms of quality, safety and efficacy, guidelines on marketing authorization of human vaccines should be consulted. Additional considerations for similar biotherapeutic products have been addressed in the guidelines for marketing authorization of similar biotherapeutic Products. Guidance on various aspects of rDNA-derived medicines is also available from several other bodies such as the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), European Medicines Agency (EMA), and the United States Food and Drugs Authority (FDA).

The requirements for marketing authorization of rDNA derived biotherapeutics shall be in accordance with the Common Technical Dossier (CTD) format as described in sections of these guidelines. The guidelines describe the format in which dossiers should be presented in support of the application for marketing authorization of biotherapeutic product. According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements, which is region specific. The Overviews and Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5. These guidelines, therefore, contain the following sections:

1. Module I: Regional administrative information
2. Module II: - Quality Overall Summaries (QoS)
   - Non-Clinical Overview
   - Clinical Overview
   - Nonclinical Written and Tabulated Summaries
   - Clinical Summary
3. Module III: Quality (Chemistry, manufacture and quality controls)
4. Module IV: Non-clinical study reports
5. Module V: Clinical study reports
6. Application Form

Information in these modules should be presented in relevant sections. Any additional data including experts' comments should be included as addenda to the relevant part, and may be provided as a supplement to, and/or incorporated into the relevant summary.

Scope

These guidelines apply, in principle, to all biologically active protein products, which are used in the treatment of human diseases prepared by recombinant DNA technology using prokaryotic or eukaryotic cells. The guidelines also apply to protein products used for in vivo diagnosis (e.g. monoclonal antibody products used for imaging), products used for ex-vivo treatment, and those intentionally modified by, for example, PEGylation, conjugation with a cytotoxic drug, or modification of rDNA sequences. Some aspects of these guidelines may apply to products produced in transgenic animals and plants. However, specific issues for such products can be found in the relevant documents published by *WHO*.

Antibiotics, synthetic peptides and polypeptides, low molecular weight heparins, Allergenic extracts, whole blood, cellular blood components and Protein products used for in vitro diagnosis are not within the scope of these guidelines.

General Information

Developments in molecular genetics and nucleic acid chemistry have made possible synthesis of highly efficient biotherapeutics products through a range of different expression systems.

Process understanding and consistency are critical since slight changes can occasionally lead to major adverse effects, such as immunogenicity, with potentially serious safety implications.

As with many other new technologies, potential safety concerns arose from the novel processes used in manufacture, from product and process related impurities, and from the complex structural and biological properties of the products themselves. Factors that have received particular attention include possible presence of contaminating oncogenic host cell DNA in products derived from transformed mammalian cells, and the presence of adventitious viruses.

Since the nature and production of these products are highly sophisticated, they require similarly sophisticated laboratory techniques to ensure their proper standardisation and control. Although comprehensive analytical characterization of the drug substance and/or drug product is expected, considerable emphasis must also be given to the manufacturing process i.e., process validation and in-process control. Adequate control measures relating to the starting materials and manufacturing process are, therefore, as important as analysis of the drug product. Thus, data on the host cell quality, purity, freedom from adventitious agents, adequate in-process testing during production, and effectiveness of test methods are required for licensing.

Glossary

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

Acceptance criteria
Means the product specifications and acceptance/ rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that is necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Anti-drug antibody
An antibody that binds to the active substance of a biotherapeutic product.

Anti-product antibody
An antibody that binds to the active substance, impurities or excipients of a biotherapeutic product.

Biomarkers
A laboratory measurement that reflects the activity of a disease process, correlates (either directly or inversely) with disease progression, and may also be an indicator of a therapeutic response. A genomic biomarker is a measurable DNA and/or RNA marker that measures the expression, function or regulation of a gene.

Biotherapeutic
A biological medicinal product with the indication of treating human diseases.

Comparability exercise
The activities – including study design, conduct of studies, and evaluation of data that are designed to investigate whether a pre-change product and a post-change product are highly similar

Critical quality attribute
A physical, chemical, biological or microbiological property or characteristic that is selected for its ability to help indicate the consistent quality of the product within an appropriate limit, range or distribution to ensure the desired product quality.

Drug product
A pharmaceutical product type in a defined container closure system that contains a drug substance, generally in association with excipients.

Drug substance
Means any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

Expiry date
The date given on the individual container (usually on the label) of a product up to and including which the drug substance and drug product are expected to remain within specifications, if stored as recommended. The expiry date is established for each batch by adding the shelf-life period to the date of manufacture.

Good clinical practice (GCP)
Means a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Good laboratory practice (GLP)
A quality system concerned with the organisational process and conditions under which non clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

Good manufacturing practice (GMP)
That part of the pharmaceutical quality assurance process, which ensures that products are consistently produced, and meet the quality standards appropriate to their intended use as required by the marketing authorization. In these guidelines, GMP refers to the current GMP guidelines published by WHO.

Immunogenicity
The ability of a substance to trigger an immune response or reaction (e.g. development of specific antibodies, T-cell response, or allergic or anaphylactic reaction).

Impurity
Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient including buffer components. An impurity may be either process- or product-related.

In-process control
Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the intermediate or product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

In-silico modelling
Computer-simulated models which are developed to model a pharmacologic or physiologic process.

Master cell bank (MCB)
An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions.

Non-human primates (NHPs)
Primates used as models for the study of the effects of drugs in humans prior to clinical studies.

Pharmacodynamics (PD)
The study of the biochemical and physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect. One dominant example is drug-receptor interactions. PD is often summarised as the study of what a drug does to the body, as opposed to pharmacokinetics which is the study of what the body does to a drug.

Pharmacogenomics
The study of the pharmacological correlation between drug response and variations in genetic elements has become of increasing importance for drug development. Such variations can have effects on the risk of developing adverse drug reactions as well as on the response to treatment. Variations in drug pharmacokinetics and metabolic pathways can cause higher drug concentrations in some patients, resulting in increased drug toxicity, and/or lower drug concentrations in some patients, resulting in decreased drug effects.

Pharmacokinetics (PK)
The study and characterization of the time course of drug absorption, distribution, metabolism and elimination. Pharmacokinetics is a quantitative analysis of how living systems handle foreign compounds.

Pharmacovigilance
The activities that are carried out after a medicinal product is marketed in order to observe and manage in a continuous manner the safety and the efficacy of the products.

rDNA-derived biotherapeutics
Biotherapeutics prepared by recombinant DNA technology, i.e. all biologically active protein products which are used in the treatment of human diseases and which are prepared by rDNA technology.

Recombinant DNA technology
Technology that joins together (i.e., recombines) DNA segments from two or more different DNA molecules that are inserted into a host organism to produce new genetic combinations. It is also referred to as gene manipulation or genetic engineering because the original gene is artificially altered and changed. These new genes, when inserted into the expression system, form the basis for the production of rDNA-derived protein(s).

Risk management plan
A detailed description of the activities that continuously ensure patients' safety and their benefit from a biological product. A risk management plan includes pharmacovigilance and many other elements.

Shelf-life
The period of time during which a drug substance or drug product, if stored correctly, is expected to comply with the specification, as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of the drug substance or drug product.

Source material/starting material
Any substance of a defined quality used in the production of a biological medicinal product, but excluding packaging materials.

Specification
Means a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Stringent Drug Regulatory Authority (SDRA)
A National Medicines Regulatory Authority which is strict, precise, exact with effective and well-functioning systems. Among others, it includes a regulatory authority which is: -

- A member of the International Council on Harmonisation (ICH) (as specified on *www.ich.org*); or an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, and Health Canada (as may be updated from time to time); or
- A regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time); or
- A Regulatory authority that has been agreed by the EMP TC to have an effective and well-functioning medicines regulation system (maturity level 3 or 4 according to the WHO-GBT).

Working cell bank (WCB)
The working cell bank is prepared from aliquots of a homogeneous suspension of cell obtained from culturing the master cell bank under defined culture conditions.

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments and Letter granting EMP TC access to assessment report), as needed.

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

For further guidance on submission procedures refer to *EMP TC Overarching Procedure.*

1.1 Comprehensive table of Content for all modules

1.2 Cover Letter

Applicant should include a cover letter in all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter shall be signed by the proposed Market Authorization Holder. A cover letter should also confirm eligibility of the product through the EMP TC as per its Guidance on Eligibility Criteria for Priority Medicinal Products.

1.3 Comprehensive table of contents

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

1.4 Application form

An application to register a biotherapeutic product must be accompanied by a completed Application Form (Annex I). The application form should be duly filled with relevant information and attachments, dated, signed and stamped appropriately.

1.5 Product Information

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

1.5.1 Summary of product characteristics (SmPC)

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

A summary of characteristics of the biotherapeutic product under evaluation should be submitted. If the Summary of Product Characteristics (SmPC), has not been approved from SRA at the time the application is submitted, a draft document may be included. The approved SmPC from SRA should then be submitted to the EMP TC as they become available.

For more guidance, refer *Guidelines on Format and Content of Summary of Products Characteristics prescribed in the EMP TC Compendia of Guidelines.*

1.5.2 Container labelling

Product should be labelled as prescribed in the Guidelines on container labelling for guidance on preparation of product labelling.

1.5.3 Package insert

Patient information leaflet (PIL): All medicinal preparations with potential for long-term use and self-administered injections and Over the Counter (OTC) must contain a patient information leaflet. Languages used for PIL and labelling should be clearly expressed in English and/or French. *Refer Guidelines on PIL for guidance on preparation of PIL.*

1.5.4 Mock-up and specimens

If the product applied for marketing authorization has a specimen or mock-up of the sample(s) presentation of the medicine available at the time of initial application should be included in section 1.4.4 of module 1.

The purpose of this is to provide an example of the product, including accessories, if any, to verify that they correspond to what is described for the characteristics of the product under evaluation.

If there are multiple strengths and/or pack sizes, one representative specimen or mock-up for each will be sufficient. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mock-ups or specimens are not available at the time of initial application, a text version may be submitted, however, mock-ups or specimens must be submitted to the EMP TC, during the evaluation process and prior to finalisation of the application.

1.6 Information regarding experts

Experts must provide detailed reports of the documents and particulars, which constitute modules 3, 4 and 5. The requirement for these signed Expert Reports may be met by providing: -

- The Quality Overall Summary, Non- clinical Overview / Summary and Clinical Overview / Summary in Module 2.
- A declaration signed by the experts in module 1.6.
- Brief information on the educational background, training, and occupational experience of the experts in Module 1.6. Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the applicant / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom.

Reports should be based on an independent assessment of the dossier and References must be provided for any additional claims not supported by the dossier. A sample declaration form is provided as *Annex II*.

1.7 Certificates of Suitability of monographs of the European Pharmacopoeia (CEP) or Regional and Continental-APIMF

If CEP is available, applicant should present a copy of CEP in section 1.7.

1.8 Certificate of Good Manufacturing Practices (GMP)

A certificate of GMP compliance should be submitted. This should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the finished biotherapeutic product, active substance(s), the diluents, and those responsible for labelling and packaging of the finished biotherapeutic product.

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

Evidence such as accredited certificate for GCP and/or GLP for the sites participating in the clinical studies should be submitted.

1.10 Regulatory Status

1.10.1 Marketing authorization status from countries with Stringent Regulatory Authorities (SRAs)

Marketing authorization status of the biotherapeutic product applied for marketing authorization in the countries with SRAs should be provided. Evidence(s) of the same should be submitted with the application.

1.10.2 Marketing authorization status in AU Member States

Marketing authorization status of the product(s) in the countries with AU should be provided. Evidence(s) of the same should be submitted with the application.

1.10.3 List of countries in which a similar application has been submitted and registered

List of countries in which a similar application has been submitted should be submitted in module 1.8.3. Dates of submission (if available) and the status of these applications should also be stated. If applicable, detailed approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case should be stated as well.

1.10.4 Statement on whether an application for the product has been previously rejected, withdrawn or repeatedly deferred in the AU Member States

A declaration whether a marketing application for the recombinant biotherapeutic product has been rejected prior to submission of the application to the EMP TC should be submitted. If the product has been rejected, repeatedly deferred, withdrawn or suspended then reasons should be stated.

1.11 Evidence of API and/or FPP prequalified by WHO

If available, the evidence indicating that the drug substance and/or drug product have been prequalified by WHO should be submitted.

1.12 Manufacturing and Marketing authorization

A Certificate of Pharmaceutical Product in the format recommended by the World Health Organization should be submitted together with a valid Manufacturing Authorization for pharmaceutical production.

1.13 Product samples

A minimum of two samples of each pack size applied for marketing authorization should be submitted together with the application. The samples should be provided in the form in which it shall appear on the market for physical evaluation.

1.14 Authorization of the Local Technical Representative

Letter issued by the applicant authorising the company to represent it and market the product in any of the African countries be submitted.

1.15 Environmental risk assessment

Evaluation of the possible environmental risks posed by the use and/or disposal of the recombinant biotherapeutic product should be submitted. In addition, proposals in that regard and the indications or warnings to be included on the product label should as well be submitted.

MODULE 2: OVERVIEWS AND SUMMARIES

The purpose of this module is to summarise the quality (chemical, pharmaceutical, and biological), nonclinical and clinical information presented in modules III, IV, and V in the market authorization application. The experts who draft these summaries should take an objective approach to the decisive points related to the quality of the product, clinical and nonclinical studies performed, report all pertinent data for the evaluation, and refer to the corresponding tables included in modules 3, 4, and 5. The information in module 2 should be presented in world format in the following order:

2.1 General table of contents

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

2.2 Introduction

A summary of the type of product, composition, mechanism of action, and indications proposed for the rDNA biotherapeutic product.

2.3 Overall quality summary

A general summary of the quality of the product should be presented, related to the chemical, pharmaceutical, and biological aspects.

This summary should refer exclusively to the information, data, and justifications included in module 3 or in other modules of the product dossier. This section should follow the format as specified in the Quality Overall Summary template *(Annex III)*.

2.4 Overview and summary of the nonclinical studies

A comprehensive and critical assessment of the results of the evaluation of the biotherapeutic rDNA production animals and in vitro testing should be presented and the safety characteristics of the same for use in humans should be defined.

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

(i) Introduction
(ii) Written pharmacological summary
(iii) Tabulated pharmacological summary
(iv) Written pharmacokinetic summary (when appropriate)
(v) Tabulated pharmacokinetic summary (when appropriate)
(vi) Written toxicological summary
(vii) Tabulated toxicological summary

2.5 Overview and summary of the clinical studies

This section should include a critical analysis of the clinical study results included in the clinical summary and in module 5. Information should include a summary of the clinical development of the product, the design of the pivotal studies, and the decisions related to the clinical studies and their performance and it should include an overview of the clinical conclusions and an evaluation of the risks/benefits in relation to the results of the clinical studies and justification of the proposed dosages.

All the data related to efficacy/effectiveness and safety assessed through the development of the product should be summarised in this section be presented, as well as any study limitations. Summaries should include all the clinical studies performed and synopsis of each study.

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

(i) Introduction
(ii) Index
(iii) Detailed discussion of the development of the product
(iv) Overview of immunogenicity
(v) Overview of the efficacy
(vi) Overview of the safety
(vii) Conclusions and risk/benefit analysis
(viii) Bibliography

2.6 Non-clinical written and tabulated Summaries

The Nonclinical Overview should be presented in the following sequence:

(i) Overview of the nonclinical testing strategy
(ii) Pharmacology
(iii) Pharmacokinetics
(iv) Toxicology
(v) Integrated overview and conclusions
(vi) List of literature references

2.7 Clinical Summary

Biopharmaceutic studies and associated analytical methods:

(i) Clinical pharmacology studies
(ii) Clinical efficacy
(iii) Clinical safety
(iv) Literature references
(v) Synopses of individual studies

In general, clinical overview and summaries should not exceed 50 pages.

MODULE 3: QUALITY (CHEMISTRY, MANUFACTURING AND CONTROLS)

3.1 Table of contents of module three

3.2.S Drug substance

The information requested under this section should be supplied individually for each active substance used in the final rDNA derived biotherapeutic product.

3.2.S.1 General information

3.2.S.1.1 Nomenclature

Information concerning the nomenclature of the active substance (e.g. proposed INN name, Pharmacopeial name, proprietary name, company/laboratory code (could include trademark name), other names or codes, if any) and identification number of production strain should be provided.

Where an International Non-proprietary Name (INN) is available for rDNA-derived biotherapeutic, the INN should be used. The proper name should be the equivalent of the INN in the language of the country of origin.

A list of any inactive substances, which may be present in the bulk active substance, should be provided.

3.2.S.1.2 Structure

The structural formula, molecular formula and molecular weight should be provided as well as the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass, as appropriate.

3.2.S.1.3 General properties

A list of physicochemical and other relevant properties of the active substance, including biological activity should be provided. The description of an rDNA-derived biotherapeutics should indicate the biological system in which it is produced (e.g. bacterial, fungal or mammalian cells) as well as the presentation of the drug product.

Refer to ICH Q6B.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The name, physical address and responsibility of each manufacturer, including contractors, and each production site or facility involved in the manufacturing and testing should be provided. The physical address should include units and blocks for each production site.

The sites or facilities involved in creation, testing and storing of the cell banks should be listed.
A valid manufacturing authorization should be provided for the production of all active substance(s). If available, a certificate of GMP compliance should be provided in the product dossier.

3.2.S.2.2 Description of manufacturing process and process controls

Information on the manufacturing process should be presented in the form of a flow diagram which indicates each step of the process including identification of the critical steps and points at which process controls are conducted.

A narrative description of the manufacturing process including information on cell bank and cell culture, harvest(s), purification and modification reaction including filling storage and shipping conditions should be provided. The in-process controls for each step or stage of the process should be indicated. Explanation should be provided on batch numbering system and any pooling of harvest or intermediates as well as scale of culture and batch

(a) Cell culture
The following information should be provided:

(i) Flow diagram from working cell bank (WCB) through harvest;
(ii) Information for each stage should be provided (population doublings, cell concentrations, volumes, pH, cultivation time, temperature) and transfers between steps.
(iii) Description of each step including any media, materials or additives used for both cell growth and for induction;
Information with respect to operating parameters for each stage with links to section 3.2.S.2.4 (in-process controls) or specifications. Detailed information with respect to
(iv) Production at infinite passage, continuous culture production and control of host-cell/vector characteristics at the end of production cycles for rDNA derived biotherapeutics can be referenced in ICH Q5D,ICH Q5B and WHO TRS 987, Annex 4.

(b) Purification
The following information should be provided:

(i) Flow diagram from crude harvest, extraction and purification to final step to obtain final active substance;
(ii) Information for each stage should be provided (pH, conductivity, processing times, hold times, elution profiles, fraction (selection) including viral inactivation step(s);
(iii) In-process controls, including acceptance criteria, should be described in detail and should be validated. Special attention should be given to the removal of viruses, nucleic acid, host cell proteins and impurities considered to pose a risk of immunogenicity;
(iv) Particular attention should be given to demonstrating the removal and/or inactivation of possible contaminating viruses and residual DNA from products manufactured using continuous cell lines;
(v) Description of each step including scale (columns, membranes), lifetime usage for resins/membranes, regeneration, buffers used, and transfer between steps;
(vi) Reprocessing steps should be described with criteria.

Further guidance on control of residual cellular DNA from continuous cell line (rDNA) and virus clearance can be obtained from *WHO TRS 987, Annex 4; http://www.who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1 and ICH Q5A.*

(c) Drug substance filling, storage and transport
The following information should be provided:

(i) Procedure used to fill active substance into container with associated process controls and acceptance criteria;
(ii) Container closure system, storage and shipping conditions;
(iii) Free/thaw or re-filtration procedures;
(iv) Hold times should be specified.

3.2.S.2.3 Control of materials

Information on raw materials used in cell culture and purification should be described with respect to raw material grade or specification, product contact filter, media composition, resins and contact membranes.

Control of source and starting materials of biological origin (viral safety information) should be summarised and detailed information should be provided in 3.2.A.2.

(a) Source, history and generation of cell substrate
A description of the host cell, its source and history, and of the expression vector used in production, including source and history, should be provided in detail.

The description should include details of the origin and identity of the gene being cloned as well as the construction, genetic elements contained and structure of the expression vector. An explanation of the source and function of the component parts of the vector, such as the origins of replication, promoters, or antibiotic markers, should be provided in addition to a restriction-enzyme map indicating at least those sites used in construction.

Further information on cell substrate source, analysis of expression construct used to genetically modify cells and incorporate in the initial cell clone for Master cell bank can be obtained in the following guidance; *ICH Q5A; ICH Q5B; ICH Q5C; ICH Q5D; WHO TSR 987, Annex 4.*

(b) Cell Banking system, characterisation and testing
Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s) should be provided in detail.

Information should include MCB and WCB, future WCB and End of Production Cell Bank and establishment of limit of in vitro cell age (LIVCA).

The type of cell bank system used, the size of the cell bank(s), the container (vials, ampoules, or other appropriate vessels) and closure system used, the methods for preparation of the cell bank(s) including the cryoprotectants and media used, and the conditions employed for cryopreservation or long-term storage should all be documented and described in detail.

For animal cells and animal derived cell banks, reference should be made to *WHO TRS 978, Annex 3.*

3.2. S.2.4 Control of Critical Steps and Intermediates

Testing and acceptance criteria for the control of critical steps in the manufacturing processes should be provided.
Stability/Micro data to support hold times of process intermediates should be provided. Supportive data to be presented in section 3.2.S.2.5

Refer to ICH Q6B.

3.2. S.2.5 Process Validation and/or evaluation

(a) Validation summaries of each unit operation, hold times, sanitary processing, and virus validation
Sufficient information on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiated selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification) should be provided. Virus validation will also need to be discussed in 3.2.A.2.

It is expected that the manufacturing processes for all active substances are properly controlled. If a biological active substance is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilisation methods. The controls used to maintain the sterility of the biological active substance during storage and transportation should also be provided. Alternate processes should be justified and described.

(b) Outline Validation strategy and scale used to complete studies
Information should include a description of the plan for conducting the study and the results, analysis and conclusions from the executed study.

(c) Reference analytical procedures used for analysis
The validation of corresponding assay and analytical methods should be cross-referenced or provided as part of justifying the selection of critical process controls and limits. For manufacturing steps, intended to remove or inactive viral contaminants, the information from evaluation studies should be provided.

Validation process should include for example: Facilities, cleaning and microbiological control, Cell growth and harvesting e.g. Cell growth kinetics and antibody productivity profiles demonstrated for each bioreactor for appropriate timeframe, Removal of media components/additives during purification and Capacity of purification process to remove contaminating virus.

Refer to EMA/CHMP/BWP/187338/2014.

3.2. S.2.6 Manufacturing Process Development

(a) Development program outline, scale(s) and tools used (design of experiment, FMEA, statistical evaluations)
The developmental history of the manufacturing process, as described in 3.2. S. 2.2, should be provided.

(b) Process description and batch information from development scale(s)

(i) **Outline any changes through development scale up to commercial (clinical batches)**
The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. non-clinical or clinical studies) including for example, changes to the process or critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale and use e.g. stability, non-clinical reference material) in relation to the change should also be provided.

(ii) **Major changes need to be assessed for potential impact on product quality**
The significance of change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance should be provided along with a discussion of the data including a justification for selection of the test and assessment of results.

(iii) **Selection of tests and results used to assess manufacturing changes during development**
Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding finished drug product(s) which may also include non-clinical and clinical studies in other modules of the submission should be included.

(iv) **Process Characterisation shall include:**

(a) Establishment of operating parameters and in process controls for commercial scale manufacture.
(b) Elimination of operating parameters/in process controls based on development work that deemed them non-critical.
(c) Freeze/thaw development data used to set the number of cycles for drug substance.
(d) Post approval – Comparability assessment of current to proposed change including side-by-side batch release data, Co-mixture analysis with reference standard and subset of initial characterisation testing to evaluation primary, secondary and tertiary structure.

It is recommended that information on study design and product knowledge should be presented in this section.

Refer to ICH Q5E and ICH Q11.

3.2.S.3.1 Elucidation of Structure and other characteristics

Details on Primary, secondary and higher order structure of product and product related substances, Post-translational forms – glycoforms information on Biological activity, Purity and Immunochemical properties (where relevant) should be provided.

3.2.S.3.2 Impurities

Information should be provided on both process and product related impurities with links back to section 3.2.S.2.2 and 3.2.S.2.4 for detailed information on removal and control of the respective impurities. There should be an Investigation of impurities (e.g. aggregates including dimers and higher multiples of the desired product).

3.2.S.4 Control of active Substance

3.2.S.4.1 Specification

At minimum release specifications for drug substance shall include appearance and description, identity, purity and potency. Information on the source, including as appropriate species of animal, type of microorganism should be included in the specifications, etc.

For initial applications, acceptance criteria shall be based on data from pre-clinical/clinical, development, consistency of the lots and stability data as appropriate. Any specification changes post approval should take into consideration clinical experience when tightening specifications.

Further requirements can be obtained in *ICH Q6 Band WHO TRS 987, Annex -appendix 2.*

3.2.S.4.2 Analytical Procedures

The analytical procedure used for testing the active substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Analytical procedure summaries should be provided that minimally includes the following subsections: Principle, Procedure and Data Analysis.

3.2.S.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Analytical method validation data should be performed to provide assurance of the method transferability to an additional testing site post initial approval.

3.2. S.4.4 Batch Analysis

Description of batches and results of three batch analyses should be provided. Results should be presented for three commercial batches against acceptance criteria. Consideration to include graphs and/or gels for those tests that are qualitative or where specification is “Comparable to Reference Material‟.

3.2. S.4.5 Justification of Specification

Justification for the active substance specification should be provided.
Rationale for use of tests for specific quality attributes taking into account the specifications and linking to manufacturing process, stability of active substance, pre-clinical/clinical studies and analytical procedures should be provided.

3.2.S.5 Reference Standard

Quality information of Reference standard or material used for testing of active substance should be provided. The information should include a description of the manufacturing process of the reference standard, and where appropriate Characterisation, stability and storage of the reference standard should also be detailed.

3.2.S.6 Container Closure system

A description of the container closure systems for the drug substance should be provided, including specifications for their component materials. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Suitability and compatibility of the materials of construct with active substance should also be demonstrated, literature reference may suffice when applicable.

3.2.S.7 Stability

Stability studies should include: Storage conditions i.e. Temperature and relative humidity for accelerated and stress Conditions.

Refer to *TRS WHO TRS 987, Annex 4, ICHQ1A and ICH Q5C.*

3.2 DRUG PRODUCT

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

For all ingredients of human or animal origin, testing results or certificates of analysis demonstrating freedom from adventitious agents should be provided as in section 3.2.A.2.

3.2.P.1 Description and composition of drug product

A description of the finished biotherapeutic product and its composition should be provided. The information provided should include:

(a) Description of the dosage form;
(b) Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any, the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)
(c) Description of accompanying reconstitution diluents (s) if any;
(d) Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable
(e) Overages need to be justified – not intended to compensate for inadequate stability or manufacturing process.

Tables provided under section 2.3.P.1 of the QOS should be used to summarise the information for this part.

3.2.P.2 Pharmaceutical development

Information and data on the development studies conducted to establish the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usage instructions as appropriate for the purpose specified in the application, should be presented. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug product quality.

Manufacturing process changes made during clinical study programme should be explained and justified. A link between formulation development and clinical batches should also be provided.
Supportive data and results from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the relevant non-clinical sections of the application. The report should include the following:

3.2.P.2.1 Drug Substance

The description and properties of the active substance should be provided. Compatibility with the rest of the components in the finished biotherapeutic product, including preservatives and other additives should be demonstrated, where applicable.

3.2.P.2.2 Drug Product

Information on the development of the formulation, considering the proposed route of administration should be provided. Details on the physicochemical and biological properties of the product, indicating the relevant parameters for developing the drug product should be included.

In addition, justification of the final qualitative/quantitative formula of the drug product should be provided.

3.2.P.2.3 Development of the manufacturing process

Description of the selection and optimization of the manufacturing process, particularly for critical aspects should be provided.

3.2.P.2.4 Container closure system selection

Information on the materials selected, protection against humidity and light, compatibility of the materials should be provided.

Information on the suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. Results of extractable study should be presented and depending on the results, also a leachable study with e.g. placebo in the final container should be presented.

3.2.P.2.5 Microbiological Attributes

Information on the integrity of the container closure system to prevent microbial contamination should be presented.

3.2.P.2.6 Compatibility

Information on the compatibility of the drug product with the manufacturing process contacts (e.g.; online filters, bags), container closure system including dosage devices where applicable and diluents should be provided.

3.2.P.3 Manufacture processes of the drug product

3.2.P.3.1 Manufacturer

Name(s), physical address(es) including unit(s) and/or block(s) and functions of each manufacturing site involved in all stages of the processes should be listed.

Valid manufacturing licence and/or certificates of GMP compliance of the sites and other pertinent organisational information for each manufacturer responsible for any portion of the manufacture or testing operations for the drug products should be provided.

3.2.P.3.2 Batch formula

Batch lot formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages and a reference to their quality standards should be provided.

3.2.P.3.3 Description of the manufacturing process

A flow diagram should be presented giving the steps of the process, indicating the points where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative of the manufacturing process, equipment and materials used, the room or area where the operation is performed (may reference the simple floor diagram), in process controls, and the critical points identified should be provided.

3.2.P.3.4 Control of critical and intermediate steps

Tests and acceptance criteria developed to identify the critical steps in the manufacturing process should be provided with justification. A listing of the in-process controls and tests performed on the product at each step should be submitted. Specifications for intermediate products should be provided and they should be followed during routine production.

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

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

A product quality review may be submitted in lieu of the information below.
The following information should be provided:

(a) A copy of the process validation protocol, specific to the biotherapeutic, that identifies the critical equipment and process parameters that can affect the quality of the product and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
(b) A commitment that three consecutive, production-scale batches of the biotherapeutic will be subjected to prospective validation in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification.
(c) Validation information relating to the adequacy and efficacy of any sterilisation process (e.g. medicinal product, packaging component should be submitted.

The process validation report should include inter alia the following:

(a) A reference to the current master production document;
(b) A discussion of the critical equipment;
(c) The process parameters that can affect the quality of the biotherapeutic (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
(d) Details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/ storage bins for uniformity testing of the final blend);
(e) The testing parameters/ acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
(f) The analytical procedures or a reference to appropriate section(s) of the dossier;
(g) The results/data obtained.

Refer to *EMA/CHMP/CVMP/QWP/BWP/70278/2012*.

3.2.P.3.6 Description of the batch identification system

Information on how the lots are defined in the stage of filling, lyophilization (if it applies) and packaging should be provided.

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

Information on the specifications for all the excipients employed in the formulation should be provided.

List of raw materials meeting in-house specifications including the tests performed and specifications of Biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephalopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product including Certificate of Suitability (CEP) should be included. The information should be provided as appendices to module 3. (3.2.A)

3.2.P.4.2 Analytical procedures

Description or bibliographic reference of the analytical methods used to control all the excipients employed in the formulation should be submitted.

3.2.P.4.3 Validation of the analytical procedures

All analytical methods used to control the excipients in the final formulation should be validated and validation reports provided if applicable.

3.2.P.4.4 Justification of specifications

Justification for the proposed specifications of the excipients should be provided.

3.2.P.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding the source/origin, description of the quality tests performed, specifications, determination of adventitious agents and viral safety.

Additionally, testing results or certificates of analysis demonstrating their freedom from adventitious agents should be provided.

3.2.P.4.6 Novel excipients

When used for the first time in a recombinant DNA derived formulated biotherapeutic product for human use or for a new route of administration, detailed information should be provided on the manufacture, characterization, and control, and data supporting safety established in nonclinical and clinical studies in relation to the drug substance used.

3.2.P.5 Control of the finished biotherapeutic product

3.2.P.5.1 Specifications of the drug product

Specifications for the drug product should be provided. At minimum, specification should contain test and acceptance criteria for description and appearance, identity, quantity, potency, purity and impurities;

For Intermediate Products (as appropriate): Highlight the list of the routine tests performed and specifications for intermediates.

3.2.P.5.2 Analytical procedures of the drug product

Detailed information on the analytical procedures used for quality control of the drug product should be provided. This section should not be presented as summaries or references.

3.2.P.5.3 Validation of the analytical procedures

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

3.2.P.5.4 Batch analysis

A description of all batches selected to assure the identity, purity, strength and/or potency, as well as the lot-to-lot consistency of the drug product and the specifications used for the drug product should be submitted.

Description should include (size, origin and use) and test result of all relevant batches e.g pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing.

Provide certificates of analysis and analytical results for at least three consecutive batches signed by authorised personnel.

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

Details on the characterization and/or determination of impurities, as applicable, depending on the nature of active substance and method used to manufacture the biotherapeutic product should be provided.

3.2.P.5.6 Justification of specifications

Justification of the proposed biotherapeutic product specifications should be provided.

3.2.P.6 Reference standards and materials

Information on the reference standards and/or materials used for testing of the finished biotherapeutic product should be provided.

3.2.P.7 Container Closure System

Detailed description of the container closure system used for the drug product plus any accessories accompanied with it should be provided. The description should include the type and form of container closure system, including the materials of which they are made and quality specifications.

Detailed information concerning the supplier(s), address(es), and the results of compatibility, toxicity and biological tests should be included.

When a delivery device is presented as part of the drug product (e.g. prefilled syringe, single-use autoinjector), it is important to demonstrate the functionality of such a combination, such as the reproducibility and accuracy of the dispensed dose under testing conditions which should simulate the use of the drug product as closely as possible.

For multi-use containers such as vials or cartridges for a pen injector, proper in-use stability studies should be performed to evaluate the impact of the in-use period of the vial or the assembled device on the formulation and the functionality of the pen injector. Dose accuracy should be demonstrated for the first and last dose delivered. In addition, the effect of multiple injections/withdrawals on the closure system should be demonstrated.

Description should also be used on the specialised devices used to monitor consistency of delivery if they are intended to become an important part of the product’s container closure system.

3.2.P.8 Stability of the Drug Product

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

Stability study report including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (temperature and relative humidity) and results for at least three lots of drug product prepared from different lots of drug substances should be provided and the reports should contain conclusions as well as proposed validity period.

A minimum of twelve months' data at the time of submission should be provided in cases where storage periods greater than six months are requested, unless otherwise justified. For storage periods of less than six months, the stability data should cover the whole proposed shelf life. The stability studies should be submitted in controlled documentation.
Stability studies under accelerated and stress conditions, including the impact of the container closure system, should also be provided.

Refer to ICH Q5C, WHO TRS 953 Annex 2 and WHO TRS 962 Annex 3.

For drug products that require reconstitution, in-use stability studies should be provided.

3.2.P.8.2 Post-approval stability program

Include the stability program or stability commitment to be carried out once the drug product is in the market, including the number of batches to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the drug product.

3.2.P.8.3 Stability data

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

The stability of each dosage form should be separately documented.

The summary results, which support the proposed expiration-dating period, under recommended conditions, in the final container and closure system, should be provided.

Stability data submitted should be for at least three consecutive batches and include the following:

(a) Information on stability of drug product, quality control methods and rationale for the choice of tests for determining stability.
(b) Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production.

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

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

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

The policy for assigning the date of manufacture of each component as well as the final product (e.g. combination formulation) and diluents, as appropriate should be described.

3.2.P.8.4 Shipping

Details should be provided on the measures used to guarantee adequacy of temperature and humidity conditions for shipping the drug product from the place of production to the place of final sale, including all the storage and distribution stages and indicating the controls performed in each of the stages. Declaration should be signed by quality control personnel.

Reference:
WHO TRS 999, Annex 2;
http://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1

3.2.A.1 Literatures References: Appendices

Provide key literatures reference used, if applicable.

3.2.A.2 Adventitious Agents Safety Evaluation

Information on control or avoidance of non-viral adventitious agents (TSE, bacteria, mycoplasma) should be supported by TSE certificates of suitability and ensure Raw material and/or production process controls in place.

Viral Adventitious Agents
Viral safety evaluation studies to demonstrate that materials are safe and approaches used to test, evaluate and/or eliminate are suitable. This shall include:

(a) Materials of biological origin – cell bank testing;
(b) Production testing;
(c) Viral testing of unprocessed bulk;
(d) Viral clearance studies – small scale demonstration of viral inactivation and removal steps used in manufacturing.

3.2.R Executed and Master batch manufacturing record

Submit Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application. In addition, submit master production document(s) for the proposed production batch size(s).

MODULE 4: NON CLINICAL TRIALS

Non-clinical studies should comply with the World Health Organization's Guidelines on Non-Clinical Evaluation, WHO Technical Series No. 9984, 2014, or most recent version.

Pre-clinical testing is a prerequisite to moving rDNA derived Biotherapeutics products from the laboratory to the clinic and includes all aspects of testing such as product characterization, proof of concept of effectiveness and safety testing in animals conducted prior to clinical testing in humans.

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

4.1 Table of contents of module four

4.2 Reports on studies

4.2.1 Pharmacology

4.2.1.1 Pharmacodynamic studies

4.2.2 Pharmacokinetics (when applicable)

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 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.)

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

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

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

Refer to ICH M3(R) and ICH S6.

MODULE 5: CLINICAL STUDIES

The clinical studies should follow the World Health Organization's Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, 2013 or most current version and ICH E6 Applicants should be familiar with these guidelines when submitting applications for marketing authorization.

This section details Particulars of tests which have been performed in human beings regarding the efficacy of the finished biotherapeutic products and the indications for which it will be used (clinical trials).

Clinical studies shall be designed and conducted to meet WHO and ICH GCP guidelines.

Tabulated summary of the clinical development program of the rDNA, in which critical parameters that may have changed during the clinical development.

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

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

Reference:
WHO TRS 987, Annex 4 Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology or most current version

WHO TRS 850 (1995) Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products or most current version.

REPORTS ON CLINICAL STUDIES

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

5.1 TABLE OF CONTENTS OF MODULE FIVE

5.2 REPORTS OF CLINICAL STUDIES

5.2.1 PHASE I STUDIES

5.2.3 PHASE III STUDIES

5.2.4 SPECIAL CONSIDERATIONS

5.2.6 PHASE IV STUDIES

6. POST MARKET SURVEILLANCE FOR rDNA DERIVED BIOTHERAPEUTIC PRODUCT

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

(a) Periodic safety update report (PSUR) in accordance to ICH Guideline E2C(R2) Periodic benefit-risk evaluation report (PBRER).

(b) Risk management plan in the format prescribed as per ICH Q 10 (Risk management plan guidelines) and WHO guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, 2013.

Annex I – Application Form for Biotherapeutic Products

Form can be accesses at *https://amrh.nepad.org/amrh-resources*

Annex II: Expert Declaration Form

The following is an example of a suitable declaration form:

Quality /Non-clinical / Clinical (delete those not appropriate)

I, the undersigned, declare that I have:

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

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

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

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

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

.....
.....
.....
.....

Annex III: Quality Overall Summary

MODULE 2.3: QUALITY OVERALL SUMMARY (QOS) Template

2.3. S Drug substance (name, manufacturer)

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

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

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

2.3.S.1.3 Physicochemical Characterization and Biological Activity

3.2.S.1.3.1 Physicochemical Characterization

3.2.S.1.3.2 Biological Activity

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

2.3.S.1.5 General description of the raw materials

2.3.S.1.6 Analytical certificates signed by the manufacturer and the applicant

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

2.3.S.2.1 Manufacturer(s)

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

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

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

2.3.S.2.2 Drug substance manufacturing process

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

2.3.S.2.3 Control of materials
(a) Source, history and generation of cell substrate
(b) Cell Banking System, characterization and testing

2.3.S.2.4 Control of critical steps and intermediates
(a) Critical steps in the process and controls performed
(b) Description of sampling procedures

2.3.S.2.5 Process validation and/or evaluation
(a) Validation summaries of each unit operation, hold times, sanitary processing and virus validation
(b) Outline validation strategy and scale used to complete studies
(c) Reference analytical procedures used for analysis

2.3.S.2.6 Manufacturing Process Development
(a) Development program outline, scale(s) and tools used (design of experiment, FMEA, statistical evaluations)
(b) Process description and batch information from development scale(s)

2.3.S.3 Characterization of the drug substance

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

2.3.S.4 Control of the drug substance

2.3.S.4.1 Specifications
2.3.S.4.2 Description of Analytical Procedures
2.3.S.4.3 Analytical Method validation
2.3.S.4.4 Batch analysis and Production consistency
2.3.S.4.5 Justification of the quality specifications

2.3.S.5 Reference standards or materials (name, manufacturer)

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

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

2.3.S.7 Stability of the drug substance

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

2.3.P FINISHED DRUG PRODUCT (NAME, MANUFACTURER)

2.3.P.1 Description and Composition

Quality Information Summary (QIS) – WHO adopted format

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

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

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

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Compatibility of Drug substance with other components

2.3.P.2.2 Adjuvant, preservative, stabilisers, and excipients

2.3.P.2.3 Development of the manufacturing process

2.3.P.2.4 Container closure system

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

2.3. P.3.1 Manufacturer(s)

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

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

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

2.3.P.3.2 Batch Formula

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

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

2.3.P.3.3 Description of the manufacturing process

(a) Flow diagram of the manufacturing process

(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

2.3.P.3.4 Controls of critical steps and intermediates

Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

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

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

2.3.P.3.6 Description of the batch identification system

2.3.P.4 Control of the adjuvant, preservative, stabilisers, and excipients

2.3.P.4.1 Specifications

Summary of the specifications

2.3.P.4.2 Analytical Procedures

Summary of the analytical procedures for supplementary tests

2.3.P.4.3 Validation of Analytical Procedures

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

2.3.P.4.4 Justification of Specifications

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

2.3.P.4.5 Excipients of Human or Animal Origin

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

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

2.3.P.4.6 Novel Excipients

2.3.P.5 Control of finished drug product

2.3.P.5.1 Specifications of the drug product

2.3.P.5.2 Analytical Procedures

Summary or references to analytical procedures

2.3.P.5.3 Validation of Analytical Procedures

Summary or references to the validation information

2.3.P.5.4. Lot consistency and analysis

(a) Description of the lots:

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

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

2.3.P.5.6 Justification of Specification(s)

3.2.P.5.7 Analytical certificates

2.3.P.6 Reference standards or materials

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

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

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

2.3.P.7 Container closure system

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

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

2.3.P.8 Stability of the finished drug product

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

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

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

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

Container closure system	Storage statement	Shelf-life

2.3.P.8.2 Post-approval stability program

Stability protocol for Primary stability batches, Commitment batches and Ongoing batches.

2.3.P.8.3 Stability Data

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

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

(c) Data to support freeze thaw cycles recommended

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

2.3.A: APPENDICES

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

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

3.2.A.3 Excipients

3.2.R Summary lot protocols