GUIDELINES FOR REGISTRATION OF BIOTHERAPEUTIC PRODUCTS

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These guidelines shall be cited as the *"Professional Guidelines on Registration Of Biotherapeutic Products,.Doc. No. PAR/GDL/016, Revision No.:0".*

Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional **Guidelines on Registration Of Biotherapeutic Products,** Doc. No. PAR/GDL/016, Revision No.:0, made this **7th day of October 2019**,that take effect on **14th October 2019**.

Signature

Dr. Medard Bitekyerezo
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PREFACE

The National Drug Authority (NDA) requires that all medicinal products intended to be marketed in Uganda meet the acceptable standards of quality, safety and efficacy and are manufactured in facilities that comply with Good Manufacturing Practices (GMP). This Guideline is to provide guidance on the registration requirements for Biotherapeutic Products in Uganda.

These guidelines apply to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines and plasma derived products and their recombinant analogues are excluded from the scope of these guidelines.

The NDA will evaluate Biotherapeutic Products before they are registered in Uganda and monitor the products once they are on the market. The NDA will also assess the suitability of Biotherapeutic Products for export from Uganda.

Submission of satisfactory data on the quality, safety, and efficacy of the Biotherapeutic Product will enable NDA to assess the suitability of the product for its intended use in Uganda. Applicants are therefore encouraged to acquaint themselves with this document before completing the registration form.

ABBREVIATIONS AND ACRONYMS

BMRs	-	Batch Manufacturing Records
CA	-	Clinical Assessor
CMC	-	Chemistry, Manufacturing and Controls
DNA	-	Deoxyribonucleic Acid
DP	-	Drug Product
DS	-	Drug Substance
EAC	-	East African Community
EMA	-	European Medicines Agency
EU	-	European Union
FMECA	-	Failure Mode Effects and Criticality Analysis
GCP	-	Good Clinical Practice
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
ICH	-	International Council for Harmonization
INN	-	International Non-proprietary Names
MOA	-	Mechanism of Action
NCE	-	New Chemical Entity
NDA-APIMF	-	National Drug Authority – Active Pharmaceutical Ingredient Master File
NMRA	-	National Medicines Regulatory Authority
NRAs	-	National regulatory Authorities
PBRER	-	Periodic Benefit-Risk Evaluation Report
Ph. Eur	-	European Pharmacopeia
PK/PD	-	Pharmacokinetic/Pharmacodynamic
RMP	-	Risk Management Plan
WHO	-	World Health Organization

GLOSSARY OF TERMS

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" means an antibody that binds to the active substance of a biotherapeutic product.

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

"Biomarkers" means 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.

"Biotherapeutics" means therapeutic biological products, some of which are produced by recombinant DNA technology

"Comparability exercise" means 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" means 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" means 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" means 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)" means a quality system concerned with the organizational process and conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

"Good Manufacturing Practice (GMP)" means 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.

"Local Agent" means a person or company with sufficient pharmaceutical expertise that is incorporated within the specific country and who will be responsible for facilitating communication with the applicant, and when the product is registered shall assume all legal responsibilities.

"Immunogenicity" means 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" means 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" means 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" means a computer-simulated model.

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

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

"Pharmacodynamics (PD)' means 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 summarized 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" means 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)" means 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" means, the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The decision to approve a drug is based on a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post-marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.

"rDNA-derived biotherapeutics" means 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" means 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" means a detailed description of the activities that continuously ensure patients' safety and their benefit from a medicinal ingredient. A risk management plan includes pharmacovigilance and many other elements.

'Shelf-life" means 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 each batch.

'Source material/starting material" means 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.

'Working cell bank (WCB)" means 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.

1.0 INTRODUCTION

Biotherapeutics are molecules derived by genetic engineering, biotechnology methods or other cutting-edge technologies. They were introduced on the market in the early 1980s, setting new milestones in modern pharmaceutical therapy that improve quality of life for many patients with life-threatening, serious, chronic and debilitating diseases.

Biotherapeutic products are large, highly complex molecular entities manufactured using living cells and are inherently variable. The manufacturing process is highly complex and critical to defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production or even transport or storage conditions may potentially result in an altered safety and efficacy profile of the final product.

Immunogenicity of a Biotherapeutic Product (BP) is of concern from clinical and safety perspective. Clinical trials and a robust post-market surveillance / pharmacovigilance plan are essential to guarantee that the product is safe and efficacious over time.

These guidelines were developed to describe the regulatory framework for BPs in Uganda, which align with current global regulation of BPs. It is intended to guide applicants on the Chemistry, Manufacturing and Control (CMC) as well as Safety and Efficacy section of a marketing application for a proposed BP.

Quality, non-clinical and clinical studies are needed to support marketing Authorization BPs. The pharmaceutical form, strength/concentration and route of administration should be the same as that used in the studies and should be manufactured in the same way. Any differences should be justified by appropriate studies.

2.0 BACKGROUND

Developments in molecular genetics and nucleic acid chemistry have enabled genes encoding of natural biologically active proteins to be identified, modified and transferred from one organism to another in order to obtain highly efficient synthesis of their products. This has led to the production of new rDNA-derived biological medicines using a range of different expression systems such as bacteria, yeast, transformed cell lines of mammalian origin (including human origin), insect and plant cells, as well as transgenic animals and plants. rDNA technology is also used to produce biologically active proteins that do not exist in nature, such as chimeric, humanized or fully human monoclonal antibodies, or antibody-related proteins or other engineered biological medicines such as fusion proteins.

There has been great progress in the ability to purify biologically active macromolecules. In addition, analytical technologies have improved tremendously since the early days of biotechnology, allowing the detailed characterization of many

biological macromolecules, including their protein, lipid and oligosaccharide components.

Together these technologies have enabled the production of large quantities of medicinal products that are difficult to prepare from natural sources or were previously unavailable. Nevertheless, it is still not possible fully to predict the biological properties and clinical performance of these macromolecules on the basis of their physicochemical characteristics alone. In addition, the production processes are biological systems which are known to be inherently variable – a feature which has important consequences for the safety and efficacy of the resulting product. Therefore a prerequisite for introducing such biological substances into routine clinical use is to ensure consistency of quality from lot to lot, and for this purpose robust manufacturing processes are developed on the basis of process understanding and characterization, including appropriate in-process controls. 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, a new set of safety issues for consideration by both industry and NRAs has been generated by these biotechnologies. 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 the 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 standardization 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.

2.1 Objective

The objective of this guideline is to guide the applicants and assessors/regulators on what needs to be submitted to support the registration (licensure/marketing authorization) of a biotherapeutic medicinal product.

2.2 Policy

These guidelines are developed in accordance with:

Section 35(3) (a) and (b) of the National Drug Policy and Authority Act Cap 206, which state that:

"Drug regulation and registration of specialities …If, on application made in the prescribed manner and on payment of the prescribed fee, the authority is satisfied —

(a) that the drug or preparation in respect of which the application is made has not previously been registered; and

(b) that the use of the drug or preparation is likely to prove beneficial, the authority shall register the name and description of that drug or preparation"; and

Section 4(2) of the National Drug Policy and Authority (Registration Regulations, 2014), which states that:

*"**Registration of drugs, preparations, vaccines and other immunological products. …** A **person who intends to manufacture, import or export a product shall,** prior to the manufacture, importation or exportation of the **product, apply to the** Authority for registration of the product."*

2.3 Scope

The guidelines apply, in principle, to all biologically active protein products, which are used in the treatment of human diseases including those 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 and NDA should be consulted for specific advice on these products.

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.

An applicant should refer to specific EMA guidance for the assessment of low molecular weight heparins

NDA would like to advise all applicants 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 application.

3.0 GENERAL INFORMATION

Developments in molecular genetics and nucleic acid chemistry have enabled genes encoding of natural biologically active proteins to be identified, modified and transferred from one organism to another in order to obtain highly efficient synthesis of their products. This has led to the production of new rDNA-derived biological medicines using a range of different expression systems such as bacteria, yeast, transformed cell lines of mammalian origin (including human origin), insect and plant cells, as well as transgenic animals and plants. rDNA technology is also used to produce biologically active proteins that do not exist in nature, such as chimeric, humanized or fully human monoclonal antibodies, or antibody-related proteins or other engineered biological medicines such as fusion proteins.

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As with many other new technologies, a new set of safety issues for consideration by both industry and NRAs has been generated by these biotechnologies. 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 is highly sophisticated, they require similarly sophisticated laboratory techniques to ensure their proper standardization 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.

4.0 MODULE I: ADMINISTRATIVE AND PRODUCT INFORMATION

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

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. English is a mandatory language for all medicinal products.

Documents should be organized in the order listed below

4.1 Comprehensive table of Contents for all modules

4.2 Cover Letter

Applicant should include a Cover Letter (Index) with 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.

4.3 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

4.4 Application form

An application to register a biotherapeutic product prepared by rDNA technology must be accompanied by a completed **Application Form (Appendix 1)**. The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.

4.5 Product Information

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

4.5.1 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 Stringent Drug Regulatory Authorities (SDRAs) at the time the application is submitted in Uganda, a draft document may be included. The approved SmPC from SDRA should then be supplied to National Drug Authority as they become available.

For more guidance refer to NDA Guidelines on Submission of Documentation for Marketing Authorisation of a Pharmaceutical Product for Human Use (CTD Format Guidelines) Format and Content of Summary of Products Characteristics for guidance on preparation of SmPC (Doc.No.PAR/GDL/004).

4.5.2 Container labeling

Product should be labeled as prescribed in the NDA Guidelines on Submission of Documentation for Marketing Authorisation of a Pharmaceutical Product for Human Use (CTD Format Guidelines) on container labeling for guidance on preparation of product labeling (Doc. No. PAR/GDL/004)

4.5.3 Package insert

Patient information leaflet (PIL): All medicinal preparations with potential for long-term use and self-administered injections and Over the Counter (OTC) medicines, must contain a patient information leaflet. Language used for PIL and labeling should be clearly expressed in English. Refer to NDA Guidelines on Submission of Documentation for Marketing Authorisation of a Pharmaceutical Product for Human Use (CTD Format Guidelines) PIL for guidance on preparation of PIL (Doc.No.PAR/GDL/004)

4.5.4 Mock-up and specimens

If the product for which registration is applied, 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 Module I.

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 provided batch number and expiry date are to be printed on the label.

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 NDA, during the evaluation process and prior to finalization of the application

4.6 Information regarding experts

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

a) The Quality Overall Summary, Non-clinical Overview / Summary and Clinical Overview / Summary in Module II

b) A declaration signed by the experts in Module I

c) Brief information on the educational background, training and occupational experience of the experts in Module I. 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.

d) 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.

4.7 Certificates of Suitability of monographs of the European pharmacopoeia (CEP) or EAC or NDA-APIMF

If CEP is available, the finished product applicant should present copy of CEP in module

4.8 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.

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

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

4.10 Regulatory Status

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

Registration status of the biotherapeutic product for which registration is applied, in the countries with SDRAs, should be provided. Evidence(s) of the same should be submitted with the application.

4.10.2 Registration status in EAC Partner States

Registration status of the recombinant biotherapeutic product applied for registration in the EAC partner states should be provided. Evidence(s) of the same should be submitted with the application.

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

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

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

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

4.11 Evidence of API and/or FPP prequalified by WHO

If evidence indicating that the drug substance and/or drug product are prequalified by WHO is available, it should be presented in Module I.

4.12 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. If available, evidence for prequalification of a biotherapeutic product by WHO should also be submitted.

4.13 Product samples

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

4.14 Authorization of the local technical representative

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

4.15 Environmental risk assessment

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

5.0 MODULE II: OVERVIEWS AND SUMMARIES

The purpose of this module is to summarize 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 III, IV, and V. The information in module II should be presented in the following order:

5.1 General table of contents

A general index should be included of the scientific information contained in modules II to V.

5.2 Introduction

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

5.3 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 III or in other modules of the registration document. This section should follow format as specified in the Quality Overall Summary template (**Appendix 2**).

5.4 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:

a) Introduction
b) Written pharmacological summary
c) Tabulated pharmacological summary
d) Written pharmacokinetic summary (when appropriate)
e) Tabulated pharmacokinetic summary (when appropriate)
f) Written toxicological summary
g) Tabulated toxicological summary

5.5 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 V. Information should include a summary of the clinical development of the product, the design of the pivotal studies, and the decisions related to the clinical studies and their performance and it should include an overview of the clinical conclusions and an evaluation of the risks/benefits in relation to the results of the clinical studies and justification of the proposed dosages. All the data related to efficacy/effectiveness and safety assessed through the development of the product should be summarized in this section 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:

a) Introduction
b) Index
c) Detailed discussion of the development of the product
d) Overview of immunogenicity
e) Overview of the efficacy
f) Overview of the safety

g) Conclusions and risk/benefit analysis

h) Bibliography

5.6 Non-clinical written and tabulated Summaries

The Nonclinical Overview should be presented in the following sequence:

a) Overview of the nonclinical testing strategy

b) Pharmacology

c) Pharmacokinetics

d) Toxicology

e) Integrated overview and conclusions

f) List of literature references

5.7 Clinical Summary

Biopharmaceutic Studies and Associated Analytical Methods

a) Clinical Pharmacology Studies

b) Clinical Efficacy

c) Clinical Safety

d) Literature References

e) Synopses of Individual Studies

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

6.0 MODULE III: CHEMISTRY, MANUFACTURING AND CONTROL

6.1 Table of contents of module three

6.2.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.

6.2.S.1 General information

6.2.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 trade mark 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.

6.2.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.

6.2.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 Topic Q6B for more details

6.2.S.2 Manufacture

6.2.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.

6.2.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;

iv. 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 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 Topic Q5D, ICH Topic Q5B and WHO TRS 987

b) Purification

The following information should be provided:

i. Flow diagram from crude harvest, extraction and purification to final step of obtaining 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 and

ICH topic 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.

6.2.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 summarized 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 ICH topic Q5A; ICH topic Q5B; ICH topic Q5C; ICH topic Q5D and WHO TRS 987 guidelines.

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 4.

6.2.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

Further requirement can be obtained in ICH Q6B

6.2.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.

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 (ies).

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 inactivate 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.

For more information, refer to EMA guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

6.2.S.2.6 Manufacturing Process Development

a) Development program outline, scale(s) and tools used (design of experiment, FMECA, statistical evaluations)

The developmental history of the manufacturing process, as described in section 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 changes should be assessed by evaluating their 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) may also include non-clinical and clinical studies in other modules of the submission should be included.

iv. Process Characterisation shall include:

Establishment of operating parameters and in process controls for commercial scale manufacture.

Elimination of operating parameters/in process controls based on development work that deemed them non-critical.

Freeze/thaw development data used to set number of cycles for drug substance.

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 topic Q5E and ICH topic Q11

6.2.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.

6.2.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).

6.2.S.4. Control of active Substance

6.2.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 topic Q6B and WHO TRS 987, particularly Appendix 2

6.2.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.

6.2.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.

6.2.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 should include graphs and/or gels for those tests that are qualitative or where specification is “comparable to reference material".

6.2.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.

6.2.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 manufacturing process of reference standard, and where appropriate Characterisation, stability and storage of the reference standard should also be detailed.

Refer to ICH topic Q6B guidelines for details of acceptability of reference standards.

6.2.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.

6.2.S.7 Stability

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

Stability studies should be done in accordance or with reference to WHO TRS 987, ICH Q1A and ICH Q5C guidelines.

6.2 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 adventious agents should be provided as in section 3.2.A.2.

6.2.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 Quality Overall Summary (QOS) should be used to summarize the information for this part.

6.2.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:

6.2.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.

6.2.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 final qualitative/quantitative formula of the drug product should be provided.

6.2.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.

6.2.P.2.4 Container closure system selected

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 final container should be presented.

6.2.P.2.5 Microbiological Attributes

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

6.2.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.

6.2.P.3 Manufacture processes of the drug product

6.2.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 organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the Biotherapeutic products should be provided.

6.2.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.

6.2.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.

6.2.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.

6.2.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 sterilization process (e.g. medicinal product, packaging component should be submitted.

The process validation report should include inter alia the following:

i. A reference to the current master production document;

ii. A discussion of the critical equipment;

iii. The process parameters that can affect the quality of the biotherapeutic, critical process parameters (CPPs) including challenge experiments and failure mode operation;

iv. 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);

v. 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;

vi. The analytical procedures or a reference to appropriate section(s) of the dossier;

vii. The results/data obtained.

Refer to EMA guideline on Guideline on process validation for finished products - information and data to be provided in regulatory submissions for more information.

6.2.P.3.6 Description of the batch identification system

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

6.2.P.4 Control of excipients

6.2.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 encephlopathies (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 III. (3.2.A)

6.2.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.

6.2.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.

6.2.P.4.4 Justification of specifications

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

6.2.P.4.5 Substances 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.

6.2.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.

6.2.P.5 Control of the finished biotherapeutic product

6.2.P.5.1 Specifications of the finished 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.

6.2.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.

6.2.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 complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.

6.2.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 authorized personnel

6.2.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.

6.2.P.5.6 Justification of specifications

Justification of the proposed biotherapeutic product specifications should be provided.

6.2.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.

6.2.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 possibleFor 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 specialized devices used to monitor consistency of delivery if they are intended to become an important part of the product's container closure system.

6.2.P.8 Stability of the Drug Product

6.2.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 topic 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.

6.2.P.8.2 Post-approval stability program

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

6.2.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.

6.2.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.

6.2.A Literatures References

6.2.A.1 Appendices

6.2.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 use 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

6.2.R Executed batch manufacturing record

Provide key literatures reference used, if applicable.

7.0 MODULE IV; NON-CLINICAL TRIALS

Pre-clinical testing is a prerequisite to moving rDNA delivered 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:

7.1 **Table of contents of module IV**

7.2 **Reports on studies**

7.2.1 Pharmacology

7.2.1.1 Pharmacodynamic studies

7.2.2 Pharmacokinetics (when applicable)

7.2.3 Toxicology

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

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

7.2.3.3 Genotoxicity

7.2.3.3.1 In vitro

7.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

7.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

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

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

7.2.3.4.3 Other studies

7.2.3.5 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.)

7.2.3.5.1 Fertility and early embryonic development

7.2.3.5.2 Embryo-fetal development

7.2.3.5.3 Prenatal and postnatal development, including maternal function

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

7.2.3.6 Local Tolerance

7.2.3.7 Other Toxicity Studies (if available)

7.2.3.7.1 Antigenicity

7.2.3.7.2 Immunotoxicity

7.2.3.7.3 Mechanistic studies (if not included elsewhere)

7.2.3.7.4 Dependence

7.2.3.7.5 Metabolites

8.2.3.7.6 Impurities

8.0 MODULE V: CLINICAL STUDIES

The clinical studies should follow the WHO TRS 987, Annex 4 guideline and ICH topic E6. Applicants should be familiar with these guidelines when submitting applications for marketing authorisation.

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 should be included.

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)

8.1 Reports on Clinical Studies

The submission in this section should be organised as summarised below

8.1.1 Table of contents of module5

8.1.2 Reports of Clinical studies

8.1.3 Phase I studies

8.1.4 Phase II studies

8.1.5 Phase III studies

8.1.6 Special considerations

8.1.7 Phase IV studies

9.0 POST MARKETING SURVEILLANCE FOR RECOMBINANT DNA DERIVED BIOTHERAPEUTIC PRODUCT

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

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

b) Risk management plan in the format prescribed as per ICH E2E (Pharmacovigilance Planning guidelines) and WHO TRS 987, Annex 4

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10.0 REFERENCES

European Medicines Agency Guideline on Process Validation for the Manufacture of Biotechnology-Derived Active Substances and Data to be provided in the regulatory submission
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-manufacture-biotechnology-derived-active-substances-data-be-provided_en.pdf

European Medicines Agency ICH Guideline E2C (R2) on Periodic Benefit-Risk Evaluation Report (PBRER)
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-0.pdf

Guidance for Industry Q1A (R2) – Stability Testing of New Drug Substances and Products
https://www.fda.gov/media/71707/download

Guideline on Process Validation for Finished Products - Information and Data to be provided in regulatory submissions
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf

Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, WHO TRS 850, Annex 3

https://apps.who.int/medicinedocs/pdf/whozip13e/whozip13e.pdf

Guidelines on Stability Evaluation of Vaccines, WHO TRS 962 Annex 3
https://www.who.int/biologicals/vaccines/Annex_3_WHO_TRS_962-3.pdf

Guidelines on the Quality, Safety, and Efficacy of Biotherapeutic Protein Products Prepared by Recombinant DNA Technology
https://www.who.int/biologicals/biotherapeutics/rDNA_DB_final_19_Nov_2013.pdf

Guidelines on the Quality, Safety, and Efficacy of Biotherapeutic Protein Products prepared by recombinant DNA Technology
https://www.who.int/biologicals/biotherapeutics/rDNA_DB_final_19_Nov_2013.pdf

ICH Guideline S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals-step-5_en.pdf

ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf

ICH Harmonised Tripartite Guideline: Quality of Biotechnological Products: Stability Testing Of Biotechnological/Biological Products Q5C
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf

ICH Harmonised Tripartite Guideline: Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process Q5E
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

ICH Harmonised Tripartite Guideline: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

ICH Topic Q5A R1 Quality of Biotechnological Product: Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-r1-viral-safety-evaluation-biotechnology-products-derived-cell-lines-human-animal-origin_en.pdf

ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-b-analysis-expression-construct-cell-lines-used-production-r-dna-derived-protein-products_en.pdf

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

ICH Topic Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological products

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf

Recommendations to Assure the Quality, Safety and Efficacy of Recombinant Hepatitis B Vaccines, TRS 978, Annex 4
https://www.who.int/biologicals/vaccines/TRS_978_Annex_4.pdf

Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products, WHO TRS 953, Annex 2
https://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityTable2.pdf

WHO Expert Committee on Biological Standardization, sixty-fourth report, TRS 987
http://apps.who.int/medicinedocs/documents/s21514en/s21514en.pdf

WHO Good Manufacturing Practices for Biological Products
https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1

APPENDIX 1: APPLICATION FOR REGISTRATION OF BIOTHERAPEUTIC PRODUCTS

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

Doc. No.: PAR/FOM/331
Revision No.: 0
Effective Date: 14 Oct 2019

Application for Registration of Biotherapeutic Products

MODULE 1: ADMINISTRATIVE INFORMATION	
1. PARTICULARS OF THE PRODUCT	
1.1.	Type of the medicinal product application New Biosimilar Renewal* * If variation has been made, information supporting the changes should be submitted. See variation guidelines for registered medicinal products.
1.2.	Proprietary Name
1.3.	International Non-proprietary Name (INN) of the Drug substance
1.4.	Strength of Drug substance per unit dosage form:
1.5.	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: Email:	
1.6.	Name and address (physical and postal) of Local Technical Representative:

(Company) Name: Address: Country: Telephone: Email:	
1.7.	Pharmaceutical Dosage form and route of administration
Dosage form:	
Route(s) of administration (use current list of standard terms)	
1.8.	Packing/pack size:
1.9.	Visual description (Add as many rows as necessary)
1.10.	Proposed shelf life (in months):
1.11.	Proposed shelf life (after reconstitution or dilution):
1.12.	Proposed shelf life (after first opening container):
1.13.	Proposed storage conditions:
1.14.	Proposed storage conditions after first opening:
1.15.	Other sister medicinal products registered or applied for registration
1.16.	Do you hold Marketing Authorization (s) of other medicinal product (s) containing the same active pharmaceutical ingredient(s) in the EAC? If yes state; Product name (s), strength (s), pharmaceutical form (s): Partner States where product is authorized: Marketing authorization number(s): Indication(s):
1.17.	Have you applied for Marketing Authorization medicinal product(s) containing

	the same drug substance (s) in the EAC? Product name (s), strength (s), pharmaceutical form (s): Indication(s):
1.18.	Pharmacotherapeutic group and ATC Code
1.19.	Pharmacotherapeutic group
1.20.	ATC Code: (Please use current ATC code)
1.21.	If no ATC code has been assigned, please indicate if an application for ATC code has been made: Yes ☐ No ☐ *(to select applicable box, double click on the box and select "checked")*
1.22.	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, the Authority reserve the right to change and/or apply only those categories provided for in their national legislation)
1.23.	Country of origin:
1.24.	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons
☐ Authorized	☐ Withdrawn (by applicant after authorization)

Country: Date of authorization (dd-mm-yyyy): Proprietary name: Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:

1.25.	List ICH countries and Observers where the product is approved.
1.26.	Name(s) and complete physical address(es) of the manufacturer(s)
1.27.	Name(s) and physical address (es) of the manufacturing site of the drug product, including the final product release if different from the manufacturer. Alternative sites should be also declared here. All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary

Name:
Company name:
Address:
Country:
Telephone:
E-Mail:

1.28.	Name(s) and physical address(es) of the manufacturer(s) of the drug substance (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should

	be listed.
Name: Company name: Address: Country: Telephone: E-Mail:	
1.29.	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance
Name: Company name: Address: Country: Telephone: E-Mail:	
1.30.	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Drug Product.
1.31.	Qualitative and Quantitative composition of the drug substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

Name of drug substance(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph standard
Name of excipient(s)			

Note: * Only one name for each substance should be given in the following order of priority: INN**, Pharmacopoeia, common name, scientific name ** The drug substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant. Details of averages should not be included in the formulation columns but should be stated below: - Drug substance(s): - Excipient(s):	
1.32.	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted
Name: Company name: Address: Country: Telephone: E-Mail:	
1.33.	Name and address (physical and postal) of the site(s) where the non- clinical studies of the product were conducted
Name: Company name: Address: Country: Telephone: E-Mail:	
2.0 DECLARATION BY AN APPLICANT	
I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge. I further confirm that the information referred to in my application dossier is available for verification during GMP inspection. I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the Authority. I further agree that I am obliged to follow the requirements of the Legislations and	

Regulations, which are applicable to medicinal products.

I also consent to the processing of information provided by the Authority.

It is hereby confirmed that fees will be paid/have been paid according to the National/Community rules*

Name: ……

Position in the company:……

Signature: ……

Date:……..

Official stamp:……..

* Note: If fees have been paid, attach proof of payment

APPENDIX 2: SUMMARY INFORMATION FOR BIOTHERAPEUTIC PRODUCT

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

Doc. No.: PAR/FOM/332
Revision No.: 0
Effective Date: 14 Oct 2019

< Name of the Biotherapeutic product >
< National Drug Authority); Date..... >

PART A - ADMINISTRATIVE INFORMATION

Sr. No.	To be completed By	1. Biotherapeutic Product Information	
1.1.	Applicant	**Name of the Biotherapeutic Product**	< Invented/Trade name >
1.2.	Applicant	**Indications for RBP**	Indications for reference biotherapeutic product in full or summary + English reference
1.3.	Applicant	**MAH**	Name and address
1.4.	Applicant	**Active ingredient manufacturing facilities and batch release site for the finished product** (if applicable)	< Name(s) and address(es) > < Confidential – Not Released >
1.5.	Applicant	**Name of the active ingredient(s)**	(INN/ Common name/ Local name/ BQ if applicable)
1.6.	Applicant	**Pharmaco-therapeutic group**	e.g. ATC code
1.7.	Applicant	**Substance category**	As described in International Nonproprietary Names (INN) for biological and biotechnological substances https://www.who.int/medicines/services/inn/BioRev2014.pdf
1.8.	Applicant	**Pharmaceutical form**	Standard Term

Sr. No.	To be completed By	1. Biotherapeutic Product Information	
1.9.	Applicant	**Quantitative composition**	Strength
1.10.	Applicant	**Route of administration**	Route
1.11.	Applicant	**Packaging/material**	Primary container
1.12.	Applicant	**Package size(s)**	Presentations available
1.13.	Applicant	**Local legal basis**	Legislative Reference
1.14.	Applicant	**Local Biotherapeutic Product guidelines**	Reference to applicable guidelines
1.15.	NDA	**Date of authorisation/licensing of Biotherapeutic Product**	Approval date for Biotherapeutic product

Sr. No.	To be completed By	2. Summary of outcomes	
2.1.	Applicant	**Quality data**	High level summary of data included in quality evaluation/analysis.
2.2.	Applicant	**Pre-clinical data**	High level summary of data included in pre-clinical evaluation.
2.3.	Applicant	**Clinical data(Pharmacokinetic, Pharmacokinetic data, safety and Efficacy data)**	Summary of included in clinical evaluation
2.4.	NDA	**Authorised indications for Biotherapeutic Products**	Indications approved following review – in full or if available in English on NDA website: provide summary and link.

PART B - SUBMITTED DATA AND REVIEWER SUMMARY

Sr. No.	To be completed by	Data required
3.1.	Applicant	**Quality data. Composition of the Biotherapeutic product(s)** Provide name of active substance and strength. Provide names (qualitative) of excipients used in formulation.
3.2.	Applicant	**Quality data. State-of-the-art methods** Include high level summary of physicochemical test methods and biological activity studies used for characterisation.
3.3.	NDA	**Quality data assessment outcome** Provide high level summary review of quality data. Specify any implications to the quality, efficacy and safety of the product.
3.4.	Applicant	**Mechanism of action** Describe mechanism of action relevant to indications applied for.
3.5.	Applicant	**Non-clinical data. *In vitro* studies** Specify dose used and length of the study.
3.6.	Applicant	**Non-clinical data. *In vivo* studies** Specify animal model(s), e.g. dose used and length of the study.
3.7.	NDA	**Non-clinical data assessment outcome** Provide high level summary review of non-clinical data and outcome including the implications to efficacy and safety of the product.

Sr. No.	To be completed by	Data required
3.8.	NDA	**CLINICAL STUDIES** **-** include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity. • Pharmacokinetic, PK • Pharmacodynamic, PD • Efficacy • Safety • Immunogenicity
3.9.	Applicant	**Clinical data. PK studies** Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
3.10.	NDA	**Clinical data. PK data assessment outcome** Provide high level summary review of PK data and outcome including how it relates to efficacy or safety of the product.
3.11.	Applicant	**Clinical data. PD studies** Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
3.12.	NDA	**Clinical data. PD data assessment outcome** Provide high level summary review of PD data and outcome including implications to the efficacy and safety of the product.
3.13.	Applicant	**Clinical data. Efficacy studies** Specify study number(s) and summary of design, population, objective and endpoint (e.g. equivalence margins), dose used and length of the study.
3.14.	NDA	**Clinical data. Efficacy data assessment outcome** Provide high level summary review of clinical efficacy data and outcome (No differences expected, however, justification may be appropriate).

Sr. No.	To be completed by	Data required	
3.15.	Applicant	**Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)	
		Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study (ies).	
3.16.	NDA	**Clinical data. Safety/ Immunogenicity data assessment outcome**	
		Provide high level summary review of clinical safety and immunogenicity data and outcome. Safety. ADRs do not pause any potential risk to the patient or the risks are low. Immunogenicity. Antibody formation in Biotherapeutic product does not pause any potential risk to the patient or the risks are low.	
3.17.	Applicant	**Additional information about the quality, safety and efficacy**	As appropriate, if not previously included.
3.18.	Applicant	**Post-authorization measures**	
		Is a risk management plan available? Which Q/ S/ E studies are included?	
3.19.	NDA	**Post-authorization measures assessment outcome.**	
		< The risk management plan (or equivalent) was considered to be acceptable. > < No additional risk management activities are foreseen post-approval.>	
3.20.	Applicant	**Availability of additional relevant information in the local language/ link**	
		As required /appropriate	

PART C - REVIEWER CONCLUSIONS

To be completed by NDA
Conclusions on Quality, Safefy, Efficacy and approval
The reviewer should comment and conclude on the following:- <The data provided by the Applicant was in line with the local legislation and guidelines.> <The data provided by the Applicant was in line with the local legislation, guidelines and international guidelines.> <u>Quality</u> All major physicochemical characteristics and biological activities of Biotherapeutic product are acceptable. <u>Non-clinical</u> Ensure that the right animal models were used and there were no major safety issues that are likely to affect humans. <u>Clinical Studies</u> The PK / PD / efficacy studies to demonstrate efficacy in patient population provided robust evidence of therapeutic relevance. Safety: The ADRs observed with biotherapeutic are outweighed by the therapeutic benefit. Immunogenicity: Antibody formation in Biotherapeutic product does not pause any potential risk to the patient or the risks are low. <u>Risk Management</u> < The risk management plan (or equivalent) was considered to be acceptable. > < No additional risk management activities are foreseen post-approval.> <u>Overall Conclusion</u> <Satisfactory assurance of quality, safety, efficacy and relevance was demonstrated using appropriate methods> <Concerns raised during the review relating to < summarise major issues > were resolved during the procedure.> The biotherapeutic product <trade name > was considered approvable.

DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
07 Oct. 2019	0	PAR/GDL/016	Mutyaba Michael Etuko Daniel Kamigisha Agnes	First Issue

End of Document