African Vaccine Regulatory Forum (AVAREF)

QUALITY ASSESSMENT

Study's full title	
Short title	
Protocol No.	
Version No.	
Investigational medical product	
Date of the review	
Reviewer's name	

Version	**Date**	**Comments**
Version 1	September 2018	Endorsed by Avaref's steering committee in Entebbe, Uganda,
Version 2	October 2019	To be tabled for adoption at the Avaref Assembly in Victoria Falls, Zimbabwe

General information for reviewers:

- Text provided in blue and in the footnotes is indicative and aims to highlight aspects that need to be taken into account during the assessment. It should be deleted prior to sending the final assessment to the sponsor
- IMPs with an MA: indicate if the IMP is going to be used according to the marketing authorization, of if the population/dose/dosing regimen/indication/duration is different. If the latter, describe the supporting information in the relevant sections
- The not applicable (NA) box should be checked off when the information is not required. A justification from the sponsor is expected in this case. The assessor is to comment on the acceptability of the information

Introduction

Workspace:

- Provide a brief overview of the quality assessment of the application, including the IMPD history
- Include a brief summary if scientific advice was provided

GMP compliance

Information on the authorization and procurement of testing laboratories can be included for IMPs derived of human tissue

Information about all manufacturers involved (drug substance, drug product, placebo, etc) and evidence of GMP (manufacturing licenses/ GMP certificates):

Name and address of site *(can be cut and pasted from the IMPD)*	**Function *(include reference to PRx, PLx etc as relevant)***	**Confirmation of valid license *(tick if provided or comment if unavailable/ not required)***	
		☐	
		☐	
		☐	
		☐	

Assessment of the IMPD (PR1, PR2 etc, replicate as required)

Delete non-relevant sections of text as required, but not the headings

The entire section 2.3, drug substance and drug product, can be deleted if the SmPC was provided and if the IMP isn't modified

Registered, non-modified product only SmPC has been provided, IMPD[1] Note: Information on the drug substance, Section 2.3, is not required	☐
Assessment of the IMPD is included in section 2.3	☐

2.3 S Drug substance

The drug substance:		
Has a monograph in	Ph. Eur. ☐ USP/JP ☐ Other ☐	No ☐
Does the active substance belong to an authorised drug product in the EU/USA/Japan?	Yes ☐ No ☐	
None of the above (full S Section is needed):		

S.1 General information

S.1.1 Nomenclature

Workspace: Paste the chemical name, other names or codes
Comments:

S.1.2 Structure

Does the submitted documentation cover this subsection adequately? Yes ☐ No ☐ NA ☐

[1] If the IMPD has not been modified for the purposes of this trial and an SmPC was submitted, then there is no need for submission of information on the drug substance and drug product

Workspace: For chemicals: paste the chemical structure / stereochemistry. For biologicals: provide a brief description of the predicted structure
Comments:

S.1.3 General properties

Does the information submitted cover this subsection adequately?	Yes ☐ No ☐ NA ☐
Workspace: • For chemicals, list the physicochemical properties likely to affect pharmacological or toxicological safety, eg solubility, pKa, etc • For biologicals, summarize the proposed mechanism of action	
Comments:	

S.2 Manufacture

S.2.1 Manufacturer(s)

See section 1.2 on GMP compliance

Are the production sites clearly identified?	Yes ☐ No ☐ NA ☐
Comments:	

S.2.2 Description of the manufacturing process and process controls

Substance: are the manufacturing processes and their controls adequately described?	Yes ☐ No ☐ NA ☐
Workspace: • For chemical IMPs, brief summary of the process including critical steps and process controls, stereochemistry of the starting materials, solvents, metal catalysts, and critical reagents. Paste the flow chart of the	

manufacturing process

- For biological IMPs, provide the flow chart of the manufacturing process including in-process testing, batch size/scale, reprocessing. Each step should be justified

Comments:

S.2.3 Control of materials

Is the control of materials adequately described?	Yes ☐ No ☐ NA ☐

Workspace:

- Include information on critical materials and their control
- For biological IMPs, include summary of source [materials], history of generation of cell substrate, the cell bank system, characterization and testing, and cell substrate stability and/or summary of source, history and generation of virus seed material
- If applicable, summary of compendial and non-compendial raw materials or materials of human origin

Comments:

S.2.4 Control of critical steps and intermediates

Is the control of critical steps and intermediates adequately described?	Yes ☐ No ☐ NA ☐

Comments:

S.2.5 Process validation and/or evaluation

Is the process validation adequately described?	Yes ☐ No ☐ NA ☐

Comments:

S.2.6. Manufacturing process development

Is the manufacturing process development adequately described?	Yes ☐ No ☐ NA ☐
Workspace: • Significant differences from the manufacturing process of toxicological or previous clinical batches should be summarized (if applicable) • For biological IMPs: comment on comparability data (if relevant)	
Comments:	

S.3 Characterisation

S.3.1 Elucidation of the structure and other characteristics

Is the drug substance sufficiently characterised?	Yes ☐ No ☐ NA ☐
Workspace: • Summarize the methods used to characterize the product	
Comments:	

S.3.2 Impurities

Are impurities sufficiently characterised?	Yes ☐ No ☐ NA ☐
Workspace: • For chemical IMPs: state if it complies with a Pharmacopeia and if so, with which one (US, EU, JP, other) or summarize the impurities from the degradation products, potential genotoxic impurities of solvents and catalysts (if applicable), residual solvents used for the purification of small molecules, and any control issues • Summarize process and product-related impurities and any issues with	

their control
Comments:

S.4 Control of the drug substance

S.4.1 Specification(s)

The specifications proposed for the drug substance, including appropriate limits, are satisfactory	Yes ☐ No ☐ NA ☐
Workspace: • For those IMPs that are not controlled by a pharmacopeial monograph, copy and paste the proposed specifications, tests methods and limits from the IMPD	
Comments:	

S.4.2 Analytical procedures

Are the analytical methods adequately described?	Yes ☐ No ☐ NA ☐
Comments:	

S.4.3 Validation of analytical procedures

Phase I trials The suitability of the methods is commensurate with the stage of development. The acceptance limits and parameters to validate the analytical methods are presented:	Yes ☐ No ☐ NA ☐
For phase II/III trials The suitability of methods is commensurate with the stage of development and clearly explained. A summary of the validation results is provided:	Yes ☐ No ☐ NA ☐
Comments:	

S.4.4 Batch analyses

Data for representative batch analyses are provided for	Yes ☐ No ☐ NA ☐

all the relevant manufacturing process, and for each drug substance manufacturer:
Workspace: • Comment on the acceptability of the batch data provided in support of the clinical trial material
Comments:

S.4.5 Justification of the specification (s)

The justification for the specifications is acceptable	Yes ☐ No ☐ NA ☐
Workspace: • Summarize the critical specifications and acceptance criteria	
Comments:	

S.5 Reference standards or materials

Reference standard A suitable reference standard is adequately described:	Yes ☐ No ☐ NA ☐
Comments:	

S.6 Container closure system

The container closure system for the drug substance is properly characterised and suitable:	Yes ☐ No ☐ NA ☐
Comments:	

S.7 Stability

The stability for the drug substance is satisfactory and properly described for all the relevant manufacturing processes:	Yes ☐ No ☐ NA ☐

Workspace:

Indicative text: amend or delete as necessary

List of proposed shelf-life/retest period and storage conditions of the drug substance.

Summary of stability studies provided in support of the proposed shelf-life. State number of months for which data is available.

Batch details (e.g. batch number)	Manufacturing process	-70ºC	-20ºC	5 °C	25°C / 60 % RH	30°C / 65 % RH	40°C / 75 % RH

Comment on whether trends or out of spec results are observed.

The extension of shelf-life will be made without substantial amendment: Yes ☐ No ☐ NA ☐

If yes, the extension will be made in accordance with a registered protocol: Yes ☐ No ☐ NA ☐

Comments:

3.3. P Drug product (repeat this section for additional IMPs)

P.1 Description and composition of the investigational medical product

The description and composition are adequate:	Yes ☐ No ☐ NA ☐

Workspace:

- Provide the qualitative and quantitative composition of the IMP

Comments:

P.2 Pharmaceutical development

The pharmaceutical development is adequately described:	Yes ☐ No ☐ NA ☐

Comments:

P.3 Manufacture

P.3.1 Manufacturer(s)

The manufacturing sites are clearly identified:	Yes ☐ No ☐ NA ☐
Workspace: • See section 1.2 on GMP compliance	
Comments:	

P.3.2 Batch formula

The batch formula is appropriately described:	Yes ☐ No ☐ NA ☐
Workspace: • Comment on the batch size proposed	
Comments:	

P.3.3 Description of the manufacturing process and process controls

The manufacturing process and process control are adequately described:	Yes ☐ No ☐ NA ☐
Workspace: • Add a brief summary of the manufacturing process including critical steps and in-process controls • Or paste the flow chart of the manufacturing process	

Comments:

P.3.4 Controls of critical steps and intermediates

The controls of critical steps and intermediates are adequately described:	Yes ☐ No ☐ NA ☐
Comments:	

P.3.5 Process validation and/or evaluation

The validation processes are adequately described:	Yes ☐ No ☐ NA ☐
Workspace: • If relevant, confirm if the process validation for non-standard sterilization and manufacturing processes are provided	
Comments:	

P.4 Control of excipients

P.4.1 Specifications

For excipients not described in current pharmacopoeias The specifications and acceptance criteria provided are appropriate:	Yes ☐ No ☐ NA ☐
Comments:	

P.4.2 Analytical procedures

The analytical procedures are adequately described:	Yes ☐ No ☐ NA ☐
Comments:	

P.4.3 Validation of the analytical procedures

The analytical procedures are adequately validated:	Yes ☐ No ☐ NA ☐
Comments:	

P.4.4 Justification of the specifications

The justification provided for the specifications of excipients and their limits is satisfactory:	Yes ☐ No ☐ NA ☐
Workspace: • Comment on the acceptability of the batch data provided in support of the clinical trial material	
Comments:	

P.4.5 Excipients of animal or human origin

The IMP contains excipients of animal origin:	Yes ☐ No ☐ NA ☐
Safety information on transmissible spongiform encephalopathies (TSE) is provided and deemed satisfactory:	Yes ☐ No ☐ NA ☐
Comments:	

P.4.6 Novel excipients

Excipients are appropriately controlled:	Yes ☐ No ☐ NA ☐
Workspace: • Confirm compliance for excipients described in the pharmacopeia. For those not described therein, check if adequate information on quality control was provided	
Comments:	

P.5 Control of the drug product

P.5.1 Specifications

Satisfactory specifications for the drug product, including appropriate limits, are proposed:	Yes ☐ No ☐ NA ☐
Workspace: • Copy and paste the proposed drug product specifications, including limits, from the IMPD	
Comments:	

P.5.2 Analytical procedures

Are the analytical methods adequately described?	Yes ☐ No ☐ NA ☐
Comments:	

P.5.3 Validation of analytical procedures

Phase I trials The suitability of the methods is commensurate with the stage of development. The acceptance limits and parameters to validate the analytical methods are presented:	Yes ☐ No ☐ NA ☐
For phase II/III trials The suitability of methods is commensurate with the stage of development and clearly explained. A summary of the validation results is provided:	Yes ☐ No ☐ NA ☐
Comments:	

P.5.4 Batch analyses

Data for representative batch analyses are provided for all the relevant manufacturing process, and for each drug product manufacturer:	Yes ☐ No ☐ NA ☐
Comments:	

P.5.5 Characterisation of impurities

The information provided for impurities is acceptable:	Yes ☐ No ☐ NA ☐
Workspace: • Discuss additional impurities/degradants that are not part of the drug substance and whether they are properly controlled by the drug product specification	
Comments:	

P.5.6 Justification of specification(s)

The justification for the drug product specifications and limits is acceptable	Yes ☐ No ☐ NA ☐
Comments:	

P.6 Reference standards or materials

Reference standard A suitable reference standard is adequately described:	Yes ☐ No ☐ NA ☐
Comments:	

P.7 Container closure system

The container closure system for the drug product is properly characterised and suitable:	Yes ☐ No ☐ NA ☐
Comments:	

P.8 Stability

P.8.1 Stability summary and conclusions

P.8.2 Post-approval stability protocol and stability commitment

P.8.3 Stability data

The drug product has undergone appropriate stability tests:	Yes ☐ No ☐ NA ☐

Workspace:

Indicative text: amend or delete as necessary

Proposed shelf-life and storage conditions of the IMP?

Summary of stability studies provided in support of the proposed shelf-life (delete/amend columns as appropriate). State the number of months for which data are available.

Batch details (e.g. batch number)	Manufacturing process	-70ºC	-20ºC	5 °C	25°C / 60% RH	30°C / 65% RH	40°C / 75% RH

Comment whether trends or out of specifications results were observed.

The extension of shelf-life will be made without substantial amendment: Yes ☐ No ☐ NA ☐

If yes, extension to be made in accordance with a registered protocol: Yes ☐ No ☐ NA ☐

Comments:

3.3 A Appendices

A.1 Facilities and equipment

Not applicable

A.2 Adventitious agents' safety evaluation

The data provided on the safety of adventitious agents are adequate	Yes ☐ No ☐ NA ☐

Workspace:

Indicative text: delete if it doesn't apply

Summarise acceptability of information provided on:

Transmissible spongiform encephalopathy agents

- Short description or list of materials from transmissible spongiform encephalopathy agents -risk species. Demonstration of compliance with PhEur 5.2.8 (relevant EDQM TSE-Certificate or adequate documentation)

Viral safety

-Identification of materials of biological origin: cell substrates, blood/tissue donations; and/or reagents: cell culture media blood; as well as excipients

-Testing of source materials: Summarise the testing regime. Is the testing regime appropriate and adequate?

-Testing of unpurified bulk: Is the strategy for routine testing adequate?

-Viral clearance studies: Is the study design according to the relevant guidelines?

-Summary of the viral clearance studies (model viruses used, viral clearance steps, total theoretical viral load)

Other adventitious agents

Comments:

A.3 Novel excipients

The information on novel excipients is in line with the respective clinical phase	Yes ☐ No ☐ NA ☐

Workspace:

- Delete this section if there are no novel excipients
- If there are, list all and cross refer to section P.4 as applicable

Comments:

A.4 Solvents for reconstitution/dilution

Information on solvents provided:	Yes ☐ No ☐ NA ☐
Workspace: • Delete this section if it's not applicable • Explain if the applicant provided enough information to support the solvents' use, eg compatibility studies?	
Comments:	

Comparator (comparator 1, comparator 2 etc – replicate individual sections of the assessment form, 2.S and 2.P as required)

The data provided for the comparator are acceptable:	Yes ☐ No ☐ NA ☐
Workspace: • For modified authorized comparators: add a description and justification of the modification	
Comments:	

Placebo (PL1, PL2 etc, - replicate this section as required)

The information provided on the placebo is acceptable: Or (delete if not applicable): No information was provided, but this is acceptable because the product has the same composition as the IMP. It's manufactured by the same manufacturer and is not sterile	Yes ☐ No ☐ NA ☐
Workspace: **Indicative text, delete if it's not applicable**	

Summary of information provided and its acceptability: *P.1 Description and composition* *P.2 Pharmaceutical development* *P.3 Manufacture* *P.4 Control of excipients* *P.5 Control of placebo product* *P.6 Container closure system* *P.7 Stability*
Comments:

Auxiliary medical products– replicate the individual sections of the assessment form, 3.S and 3.P as required

The quality data provided for non-authorised auxiliary medical products are acceptable	Yes ☐ No ☐ NA ☐
Workspace: **Indicative text, delete if it's not applicable** ***3.S*** ***3.P***	
Comments:	

Labelling

Is the proposed labelling in line with national requirements?	Yes ☐ No ☐ NA ☐
Comments:	

Blinding

Workspace: • Refer to the statistical methodology given in the clinical trial protocol
Comments:

Assessor's overall conclusions on the quality part

The quality data are acceptable:	Yes ☐ No ☐
Supplementary information has to be provided Refer to the requests for additional information	Yes ☐ No ☐
Overall comment/ conclusion on the quality assessment:	

Requests for additional information on quality