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## GUIDELINE FOR PRE-REGISTRATION CONSULTATION MEETING

This document provides guidance on the procedures involved in the scheduling and conduct of Pre-Registration Consultation meetings between the Office of the Chief Regulatory Authority (CRO) of the South African Health Product Regulatory Authority (SAHPRA), and the applicant / sponsor for biological medicines. The primary purpose of the meetings is to address issues relating to the development of biological medicines in the planning phase of such products.

Guidelines and application forms are available from the office of the CRO and on the SAHPRA website.

### Document History

Final Version	Reason for Amendment	Effective Date
1	First issue and published for implementation	March 2015
2	Editorial and Format Changes	May 2020
3	<ul style="list-style-type: none"><li>- Content structured on the new SAHPRA Guideline Template</li><li>- Old document number 2.39 changed to SAHPGL-PEM-BIO-03</li></ul>	September 2022

**DR BOITUMELO SEMETE-MAKOKOTLELA**  
CHIEF EXECUTIVE OFFICER

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## Glossary

Abbreviation/ Term	Meaning
Applicant/Developer/Sponsor	The legal entity (or agent) that applies for the permit to conduct clinical trials, and eventually for the registration of the new biological medicine.
Pre-Registration Consultation (PRC) Meeting	Meeting requested by developer at the point where the manufacturing process for a potential product has reached a point of consistency and has a potentially defined presentation/indication, but further development could benefit from the advice of regulatory experts on the pre-clinical or clinical development plan. The consultation might enable applicant/s to submit dossiers containing appropriate information in line with the CTD format, which may lead to an appropriately constructed dossier that will enable a decision on registration of a biological medicine.
Pre-Registration Consultation Expert Committee (PRCEC)	Core team of regulatory reviewers focused on the quality and clinical development of a particular product, providing the core input to both the Clinical Trials Committee (CTC) and Biological Medicines Committee (BMC) when the application comes up for review. The EC operates separately from the CTC. It predominantly focuses on product development, leaving issues of trial conduct and relevant ethics review bodies to the CTC.
Pre-Registration Consultation (PRC) Meeting Material	Dossier to be compiled and submitted before a consultation meeting is conducted.
Pre-Registration Consultation (PRC) number	Unique number identifying the product/presentation, including the dossier submitted for a Pre- Registration Consultation meeting. Each communication from MCC to applicant gets the PRC plus a suffix number identifying the sequence of communication, e.g. 334455/001, 334455/002.
Point of Contact (POC)	Person at SAHPRA identified as responsible to assist the applicant with the procedure to schedule and coordinate a meeting.

## 1. INTRODUCTION

SAHPRA through its Biological Medicines Unit has developed this guideline to address the need of applicants and/or sponsors to consult the regulator prior to registration of the Biological product.

### 1.1. Purpose

The purpose of this guidance document is to describe the procedures involved in the scheduling and conduct of Pre-Registration Consultation (PRC) meetings between the Office of the CRO of the SAHPRA and the applicant / sponsor of biological medicines. The primary purpose of the meetings is to address issues relating to the development of a product in the planning phase of such products.

### 1.2. Scope

This guideline applies to the scheduling of a PRC meeting by the parties involved in the development or manufacturing of biological medicines that have not been previously submitted for registration to the MCC, or to any other regulatory authority and for which registration may be sought from the MCC in the future.

PRC meetings with industry provide a forum for SAHPRA to provide guidance to organizations during product development and facility design, and to facilitate their compliance with the regulations governing the development of products.

This should be limited to local manufacturers and developers of biological medicines, including vaccine developers where the major part of the clinical development will be in a South African population.

Meetings should serve a useful purpose and should not be premature or clearly unnecessary. In order to guide the meeting, a checklist is to be submitted with the request for a meeting.

## 2. LEGAL PROVISION

Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended and the relevant Regulations.

## 3. TYPES OF PRC MEETINGS

Summary: Three types of meetings have relevance.

Type A: meeting conducted before finalization of non-clinical tests. This is not a formal submission.

Type B: meeting conducted when non-clinical development is complete and Ph-I trials are ready for submission. This is a formal submission.

Type C: These meetings are held during the clinical development phase and prior to final registration application.

### 3.1. TYPE A

- a. To review and reach agreement on the format of application.
- b. Design of animal studies needed to support human clinical testing and product characterization issues.
- c. The scope and design of planned Phase I studies.
- d. Facility design.
- e. General product issues.

### 3.2. TYPE B

- a. Depict for reviewers the general information to be submitted in the registration application.
- b. Discuss preliminary efficacy results derived from studies conducted to support registration process and appropriate methods for final statistical analysis.
- c. Discuss the proposed format for data in the planned marketing application.
- d. To identify the studies that the sponsor/applicant will rely on as adequate and well-controlled.
- e. Plans to assess paediatric safety and effectiveness.
- f. To discuss submission of an incomplete application.
- g. To discuss any major outstanding issues.

### 3.3. TYPE C

To discuss the Phase II or Phase III clinical development of a proposed Medicinal Product. The PRC EC would typically conduct this, with attendance by CTC members.

#### 3.3.1. End of Phase I / Pre-Phase II meeting

- a. To review Phase I clinical testing data.
- b. To reach agreement on design of Phase II controlled clinical trials, with the aim that such testing will be adequate to provide sufficient data on the medicine's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the biological medicine in paediatric patients.

#### 3.3.2. End of Phase II / Pre-Phase III meeting

- a. Review Phase II data to determine if it is safe to proceed to Phase III.
- b. To evaluate plans for the Phase III program and protocols.
- c. Plans to assess paediatric safety and effectiveness.
- d. To identify any additional information necessary to support a registration application for the uses under investigation.

## 4. PROCEDURE FOR REQUEST TO SCHEDULE MEETINGS

- 4.1. All communications regarding meetings, as defined in this document, should be forwarded to the CRO's office.
- 4.2. All meetings must be preceded by the submission of a written application to the CRO of Medicines and be accompanied by the necessary discussion materials.
- 4.3. Approximate lead-time for submission of information package in CTD format is approximately one (1) month before the scheduled meeting with the Expert Committee.
- 4.4. Every effort to respond to meeting requests will be made by SAHPRA as expeditiously as possible.
- 4.5. Upon receipt of a request for consultation with the relevant Expert Committee of the SAHPRA, the CRO will appoint an appropriate qualified Panel (max 6 persons) to conduct the consultation.
- 4.6. Meetings may either be face-to face (in person) or electronic i.e. teleconference or video conference/Skype.
- 4.7. Meetings will be strictly limited to one (1) hour and will result in a verbal response from the panel at the conclusion of the meeting.
- 4.8. These responses are non-committal and are non-binding on the CRO or on SAHPRA.

## 5. PRE-REGISTRATION CONSULTATION MEETING MATERIAL

A completed PRC meeting Material Checklist must be submitted with the application.

The CHECKLIST is to be used for the preparation of a formal request to the office of the Chief Regulatory Officer (CRO)/ South African Health Product Regulatory Authority (SAHPRA) for the purpose of the meeting and should be submitted to the SAHPRA.

**NOTE:** Information to be submitted as:

- Covering letter explaining briefly the substance of the application;
- 1 x Hardcopy of all documents for filing;
- 1 x Hardcopy of 1 & 2 (below) plus ALL on CDs sufficient for each panel member (Max 6)

Item		✓
1	<b>MEETING AGENDA</b>	
	Indicate Type of Meeting requested e.g. A, B or C (Guideline: 20 minutes for scientific presentation; 30 minutes for discussion; 10 min for Expert Committee Panel Response)	
2	<b>LIST</b> of expected participants and personal profile [1 page per person]	
	<b>LIST</b> of the specific objectives of outcome that the applicant expects	
	<b>LIST</b> of specific questions to the Expert Committee	
3	<b>1. PRODUCT DOSSIER:</b>	
	<ul style="list-style-type: none"> <li>• Cover page containing the following information:</li> <li>• Name, Address, and contact information of Sponsor;</li> <li>• Name of the Product;</li> <li>• Date of submission;</li> <li>• Identification of the pre-phase;</li> <li>• Name and title and contact information of the person responsible for monitoring the progress of the application; and</li> <li>• Signature of the Sponsor of sponsor's authorized representative</li> </ul>	
	2. Page 2, Table of Contents	
	3. Page 3 to end, Information as required for each pre-phase in an accurate and complete English version, created in Arial 11 font, and single spacing.	
	4. Information previously submitted: The sponsor is not required to submit information previously submitted but may incorporate the information by reference. The reference must be identified by name, reference number, volume and page number where the information can be found.	
3.1	<b>Pre-Phase I</b> (Limited to 30 A4 pages)	
3.1.1	Description of product, including scientific rationale and chemical or biochemical characterization	
3.1.2	Description of the manufacturing facility ( <i>including status of facility e.g. certified for GMP; ISO 9001, etc.</i> )	
3.1.3	Summary of the manufacturing process including:	
	a. A flowchart;	
	b. A description of the manufacturing process;	
	c. A description of the source and quality of starting materials;	
	d. A description of in-process testing (e.g. quality controls {identity, assay, purity, impurities profile}); and	
	e. Tentative lot-release specifications [descriptions of identity, purity, sterility (e.g. sterilization process, release sterility and endotoxin testing, if applicable), stability, general safety and potency)	

3.1.4	Summary of pre-clinical data of the proposed vaccine that support a clinical study, including:	
	a. Safety studies; and	
	b. Activity studies (e.g. immunogenicity studies, neutralization assays, and investigations in animal protection models) ( <i>linkage of pharmacological and/or toxicological batches to trial batches</i> )	
3.1.5	Summary of the proposed Phase I study protocol to include:	
	a. Description of study subjects;	
	b. Inclusion / exclusion criteria;	
	c. Statistical considerations; and	
	d. Safety monitoring	
	<i>(Do not include information on study sites, Investigator's CVs, insurance, and informed consent procedures)</i>	
3.1.6	List of questions or issues for discussion e.g.:	
	a. Formulation issues	
	b. Toxicology study design	
	c. Use of a novel excipient	
	d. Adequacy of in-process or lot release tests	
	e. Phase I trial design, and	
	f. Proposed label indication	
3.2	<b>Pre-Phase II</b> [Limited to 40 A4 pages]	
3.2.1	Description of product, including scientific rationale and chemical /biochemistry characterization	
3.2.2	Description of the manufacturing facility ( <i>including status of facility e.g. certified for GMP; ISO 9001, etc.</i> )	
3.2.3	Summary of the manufacturing process including:	
	a. A flowchart	
	b. A description of the manufacturing process	
	c. A description of the source and quality of starting materials	
	d. A description of in-process testing, and	
	e. Tentative lot-release specifications (descriptions of identity, purity, sterility, stability, general safety and potency)	
3.2.4	Summary of pre-clinical data of the proposed vaccine that support a clinical study, including:	
	a. Safety studies; and	
	b. Activity studies (e.g. immunogenicity studies, neutralization assays, and investigations in animal protection models)	
3.2.5	Summary of the proposed Phase II study protocol including:	
	a. Design	
	b. Description of study subjects	
	c. Inclusion / exclusion criteria	
	d. Statistical consideration	
	e. Efficacy endpoints and correlates of protection, and	
	f. Safety monitoring	
	<i>(Do not include information on study sites, Investigator's CVs, insurance, and informed consent procedures)</i>	
3.2.6	List of questions or issues for discussion e.g.:	
	a. Formulation issues	
	b. Toxicology study design	

	c. Use of a novel adjuvant	
	d. Adequacy of in-process or lot release tests	
	e. Phase II trial design	
	f. Target population in South Africa	
	g. Measures of efficacy and safety	
	h. Proposed label indication, and	
	i. Package inserts	
3.3	<b>Pre-Phase III</b> (Limited to 50 A4 pages)	
3.3.1	Description of product, including scientific rationale and chemical /biochemistry characterization	
3.3.2	Description of the manufacturing facility ( <i>including status of facility e.g. certified for GMP; ISO 9001</i> )	
3.3.3	Summary of the manufacturing process including:	
	a. A flowchart	
	b. A description of the manufacturing process	
	c. A description of the source and quality of starting materials	
	d. A description of in-process testing	
	e. Tentative lot-release specifications (descriptions of identity, purity, sterility, stability, general safety and potency).	
3.3.4	Summary of pre-clinical data of the proposed vaccine that support a clinical study, including:	
	a. Safety studies; and	
	b. Activity studies (e.g. immunogenicity studies, neutralization assays, and investigations in animal protection models)	
3.3.5	Detailed description of Phase I safety data and Phase II safety and efficacy data	
3.3.6	Previous human data relevant to the product (or similar products), if available, including relevant immunogenicity of efficacy data as appropriate.	
3.3.7	Summary of the proposed Phase III study protocol to include:	
	a. Design	
	b. Description of study subjects	
	c. Inclusion / exclusion criteria	
	d. Statistical considerations	
	e. Efficacy endpoints and correlates of protection, and	
	f. Safety Monitoring	
	<i>(Do not include information on study sites, investigators CVs, insurance, informed consent procedures)</i>	
3.3.8	Summary of data on the product that support its clinical application in human subjects	
3.3.9	List of questions or issues for discussion e.g.:	
	a. Formulation issues	
	b. Trial design	
	c. Measures of efficacy and safety	
	d. Target population in South Africa, and	
	e. Proposed package inserts	



## 6. CANCELLATION OF MEETING

- 6.1. The POC must clearly convey to the Applicant that all the pre-read meeting material (Dossier) should be received not less than one (1) month prior to the scheduled meeting.
- 6.2. The applicant should also be notified that failure to submit adequate meeting materials by the appropriate date could result in cancellation.
- 6.3. Meetings may be postponed or cancelled by either party based on sufficient cause. All parties need to be immediately notified and a cancellation notice shall be forwarded in writing by e-mail via the CRO's office.

## 7. THE MEETING

- 7.1. The POC shall ensure that a clear agenda and adequate materials are available for the PRC meeting.
- 7.2. The agenda for the sponsor /applicant's question and SAHPRA responses as generated in the internal pre-meeting.
- 7.3. The meeting will begin with introductions.
- 7.4. The appointed meeting leader or rapporteur will keep the meeting to the agenda with attention to the time allotted and summarize issues and /or agreement reached at the conclusion of the meeting.
- 7.5. In order to decrease misunderstandings, it is strongly recommended that the last 5 – 10 minutes of the meeting be used to summarize agreements reached, advice provided, action items, and unresolved issues.
- 7.6. **Minutes of the meeting.**
  - 7.6.1. The secretariat will not provide minutes of the meeting to the applicant but will retain notes for own use as compiled by the POC.
  - 7.6.2. The applicant takes minutes for own reference and also submit such to the POC for approval as a true reflection of proceedings.
  - 7.6.3. In exceptional cases, the Panel / Expert committee may need to respond to the applicant in writing or in a follow-up meeting. Written material will take the form of an Expert Opinion or Advisory Statement.
  - 7.6.4. In the event of the Developer intending to submit a Clinical Trial Application to the CTC following consultation with the PRC EC; the PRC EC report will be provided to CTC.

## 8. REFERENCES

The following related documents are referenced:

- 8.1. Guidance for Industry. Formal Meetings Between the FDA and Sponsors or Applicants <http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf>
- 8.2. Formal FDA Meeting Request: Guidance and Template (contains further links to relevant FDA guidance documents) <http://ictr.johnshopkins.edu/wp-content/uploads/import//1331-FDA%20Formal%20Meeting%20Guidance%20and%20Template.pdf>
- 8.3. Pre-IND Meeting Checklist (contains further links to relevant FDA guidance documents) [http://icahn.mssm.edu/static\\_files/MSSM/Files/Research/Resources/Office%20of%20Clinical%20Resea](http://icahn.mssm.edu/static_files/MSSM/Files/Research/Resources/Office%20of%20Clinical%20Resea)

[rch/PreIND-Meeting-Checklist.pdf](#)

- 8.4. European Medicines Agency Guidance for Companies requesting Scientific Advice and Protocol Assistance  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004089.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004089.pdf)  
  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000049.jsp&mid=WC0b01ac05800229b9](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9)
- 8.5. CHMP <Protocol Assistance> <Scientific Advice> Briefing Document Template(18/06/2010)  
[Template letter of intent for request of scientific advice or protocol assistance\(08/11/2012\)](#)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Template\\_or\\_form/2009/11/WC500011910.p df](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/11/WC500011910.pdf)

## 9. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the old guideline for Biological Medicines Pre-reg Consultation Meeting, document number 2.39. It will be reviewed on this timeframe or as and when required.