SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDANCE ON GOOD PRACTICE (GxP) INSPECTIONS DURING EMERGENCIES/DISASTERS INCLUDING THE COVID- 19 PANDEMIC

This document has been prepared to serve as a recommendation for the conducting of good practice (GxP) inspections during emergencies/disasters including the COVID- 19 pandemic. It represents the South African Health Products Regulatory Authority's current thinking on this subject. This guidance should be read in conjunction with the SA Guidelines for Good Manufacturing/Clinical/Wholesale Practices.

CHIEF EXECUTIVE OFFICER

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1. Introduction

1.1 With the complexity of global supply chains, the demand for inspecting pharmaceutical facilities and clinical trial sites far exceeds what any Regulatory Authority can accomplish during emergencies/disasters including the COVID- 19 pandemic and a framework is required to assist Regulators in managing quality risks posed by the increasingly complex pharmaceuticals global supply chain and clinical trials.

1.2 GxP inspections are conducted for purpose of product registration and also for the purpose of the system of licensing the manufacturing and distribution of medicinal products. An informed decision on the GXP compliance of manufacturing / distribution/ importation/ exporting/ of medicines and of the conduct of clinical trials can be made, in certain circumstances, based on the outcome of virtual or remote inspection by the Regulatory Authority or Authorities.

1.3 Confirming GxP compliance through virtual/ remote inspection, where appropriate, without undertaking an onsite inspection could potentially ensure:

a) The periodic re-evaluation or re-assessment and monitoring of medicines, medical devices and IVDs,

b) Compliance with existing legislation is controlled through a process of active inspection and investigation and

c) Assessment of clinical trial protocols according to prescribed ethical and professional criteria and defined standards.

1.4 This Guideline sets out appropriate steps for meeting the responsibility of importation, manufacturing, sale of medicine and the conduct of the clinical trials during emergencies/disasters including the COVID- 19 pandemic.

1.5 This document should be read in conjunction with the Guidelines on Good Manufacturing Practice, Good Wholesaling Practice and Good Clinical Practice.

a) This guideline supports legislative requirements as outlined in the various Acts.

b) SAHPRA ensures that medicines meet the requirements of quality, safety and efficacy.

c) Medicines should comply with the information that has been evaluated and approved by the SAHPRA.

2. Purpose

This guide is for prospective SAHPRA license holders. It provides guidance on the inspection processes to be undertaken during unexpected emergencies/disasters including the COVID- 19 pandemic. It is important to understand it cannot replace an on-site auditor's scrutiny and is an interim measure. This guidance is established to handle and conduct remote audits in cases of travel restriction due to unexpected events / circumstances that prevent an on-site audit. **There will be a greater emphasis on the quality of the self- inspection programme, which should continually be handled as per approved procedures at the facility/ site.**

These guidelines are defined for inspection during emergencies/disasters including the COVID- 19 pandemic and focusses on the good practices (GxP) evidence and the regulatory requirements for conducting pharmaceutical clinical trials, wholesaling, importation (holder of certificate of registration), distribution, and manufacturing for SAHPRA license /approval holders.

3. Scope

This guidance document outlines how to submit evidence and what evidence will be required to be submitted to support facilities level of compliance with GxP requirements during emergencies/disasters including the COVID- 19 pandemic inspection. SAHPRA will assess the evidence against GxP standards according to the Act and its associated regulations. These guidelines for the GxP inspection of medicine and applies equally to products for human and for veterinary use as per Act 101 during emergencies/disasters including the COVID- 19 pandemic c. The sequence of doing these audits across the GxP spectrum will depend on the readiness level of systems both at SAHPRA and at facilities/ sites.

This document clarifies the functions and requirements of good practice for:

a) Pharmaceutical Holder of Certificate of Registration,
b) Pharmaceutical Manufacturers,
c) Pharmaceutical Wholesalers,
d) Pharmaceutical Quality Control Laboratories and
e) Clinical Trials Sites

A remote audit is an audit which is performed under a confidential disclosure agreement as applicable via remote tools (examples include: landline or mobile telephone, e-mails, Skype, WhatsApp, Zoom, Microsoft Teams etc.), with the exchange of electronic documents using internet-cloud system when the size of document cannot be transferred by direct mails (e.g. WeTransfer, Dropbox, Mimecast). There is a preference from SAHPRA to review documents within a web-based documentation system.

A remote audit is different from a questionnaire assessment or teleconference as there should be a direct discussion between the auditor and the auditee. The use of a video-conferencing system is considered as essential. The auditor shall have the opportunity to read and assess written audit evidence; therefore, the use of shared screen is encouraged as well. The auditor may also be granted temporary secure access to the organisation's electronic validated GxP IT systems to observe information and directly.

A confidentiality agreement is essential for the following considerations:

a) The realisation of a remote audit does need to exchange documents, data, videos and photographs through internet-based virtual support software. Therefore, both the auditor and the auditee shall accept to share information for the purpose of the audit only and

b) There should be a prior commitment to keep confidential information shared before and during the audit, and to make auditee aware of storage and archiving of any photographs, videos or documents provided by the auditee.

It shall be agreed during the audit preparation phase, the communication tools to be used, and their connection and availability to both sides. The ability to exchange documents should be tested a few days before the audit. The inspection programme will be conducted in three phases to allow for controlled and smooth process. Inspection scheduling to the applicant will be via emails, telephonic communications and a proposed inspection plan and document list will be submitted. The phases are as follows:

Phase 1*	1. Company declaration document and confidentiality agreement document	**SAHPRA - Site/Facility**
	2. Company application form and SMF	
	3. Notification letter and proposed inspection plan	
	4. Company Corrective Actions and Preventative Actions (CAPA's) from last inspection	
	5. Virtual opening meeting	
	6. Discussions about documents listed on the inspection plan	
	7. Closing of Phase 1 (acknowledgement letter)	
Phase 2	Desktop Inspection/Review	**SAHPRA**
Phase 3	Remote Virtual Inspection: The auditor will connect with the auditee on the agreed secure remote virtual communication platform (landline or mobile telephone, e-mails, Skype, WhatsApp, Zoom,	**SAHPRA - Site/Facility**

	Google Teams etc.). The auditor shall provide the site/facility with feedback from Phase 2: Desktop Inspection/Review and will provide the site/ auditee the opportunity to present more evidence and/or additional evidence of procedures/processes to address noted gaps or deficiencies. Furthermore, issues with regards to inspection report, response review and inspection fees will be discussed.	

**The individual sequence of phase 1 can change to facilitate ease of audit*

4. Submission and assessment of documentary evidence and information

The organisation, when subject of a remote audit should ensure that auditee representatives for each topic and each function is available. Therefore, the continuous communication between the auditor and the auditee's Team Leader is crucial for adapting the agenda continuously.

a) Submission documentary evidence

Submissions of the requested documents in the inspection for each site should be submitted or access granted to web based documentation system by the Responsible Pharmacist (RP)or Principal Investigator (PI) to SAHPRA.

b) Assessment of documentary evidence and information

Desktop assessment (and remote virtual inspection) involves a detailed evaluation of the specified documentary evidence supplied by the site/facility against GxP guidelines and regulations as determined by the Authority.

c) General requirements for documents

Documents to be submitted to SAHPRA as evidence of compliance to GxP standards and systems that are implemented at the facility should adhere to the following general requirements:

a) All certificates and other supporting documents should be in English,
b) Where the document is not in English, it should be submitted with a certified translation,
c) A signed and dated statement by the certified translator, stating that each document is a true and accurate translation of the original document, must accompany translated documents,
d) Submitted documents should be the most recent and reflect current activities and practices and approved and dated accordingly (draft, expired or superseded documentation cannot be used) and
e) Documents must provide sufficient information to cover the scope of activities for which

confirmation of GxP compliance is to be determined.

All documents, whether the original format is paper or electronic, are to be submitted electronically (for example as Electronic transfer systems, DVD's, CDs etc.) and are not required to be certified as original copies. Certification of a document may be requested if, for example, there is concern over the validity of the supplied documents. SAHPRA can request certified copies of original documents at any time.

5. Authenticity of documents

It is important that documentary evidence provided by the applicant as the basis for granting approval for good practices be current, accurate and authentic. It is the responsibility of the auditee to ensure this. The RP/PI should include a cover letter with the application making a **declaration** that all the documents submitted are authentic, accurate and correct.

Submission of inaccurate or false information may result in declaration of the manufacturer, wholesaler, distributor, holder of certificate of registration or quality control laboratory as non-compliant and possible rejection of registration/variation application, possible rejection of license renewal, possible suspension/cancellation of license or possible suspension of clinical trial.

6. Failure to submit documentary evidence

If the auditee is unable to provide adequate documentary evidence, including information on current compliance, or to submit the documents before a specified deadline or fails to submit documents as required, the Authority will issue non-compliance resolution. In such circumstances, approval of GxP should only be granted after the on-site inspection has been conducted, and the manufacturer, holder of certificate of registration, outsourced quality control laboratory, wholesaler or distributor has been found compliant.

7. Responsibilities of the Facility/Site

The main responsibilities of the facility/site for GxP compliance inspection during emergencies/disasters including the COVID- 19 pandemic are summarized below:

a) Ensuring that all required evidence documents are submitted during GxP compliance inspection. Incomplete submissions will be rejected, and the facility/site will be required to reapply with payment of prescribed fees,
b) Ensuring that all necessary arrangements are in place to ensure uninterrupted video conference interviews and electronic access to QMS as required,
c) Remitting the application for inspection and fee(s) prior to the GxP inspection if applicable and
d) Remitting the fees on submission of the report from SAHPRA to facility/site.

8. SAHPRA Assessment of the GxP evidence

After SAHPRA's assessment of the GxP evidence, a resolution will be assigned to the facility/site:

a) Compliant – issued when the evidence is deemed acceptable and demonstrates GxP compliance.
b) Non- compliant – issued when the evidence is deemed unacceptable and does not demonstrate GxP compliance.

Terms and conditions may be added to the Regulator resolution if other factors (such as the facility's compliance history, drug type, medical necessity, category, dosage form or activities conducted at the facility) require additional GxP oversight.

9. Remote Audit Times

Please be aware that these times in the below table are not fixed and the process will be refined as we perform the inspections.

We provide target processing timelines for during emergencies/disasters including the COVID- 19 pandemic inspection process to assist industry in planning their regulatory activities. The timelines are effective from the date of the scheduling letter by the auditor. The table below outlines the current target processing timelines (working hours). Any changes to these that occur due to the reasons outlined above will be communicated via the notices about emergencies/disasters including the COVID- 19 pandemic website or SAHPRA website.

Day	Phase	SAHPRA	Timelines	Industry (Facility/Site)	Timelines
Day 1	**Phase 1**	Scheduling	-	Response	2 (two) Hours
		Virtual: Opening Meeting	2 (two) hours	Virtual: Opening Meeting	2 (two) hours
		Documents Request Letter	-	Response	1 (one) Hour
		Request Letter (Additional Evidence/ Documents request)	-	Response	1 (one) hour
		Acknowledgement	2 (two) hours		
Day 1 - 3	**Phase 2**	Desktop Inspection/ Review	16 (twenty) hours		
		Confirming Virtual Remote Inspection		Response	1 (one) hour
Day 4 - 5	**Phase 3**	Virtual Remote Inspection	16 (sixteen) hours	Virtual Remote Inspection	16 (sixteen) hours

10. Emergencies/disasters including the COVID- 19 pandemic inspection process fees

a) Phase 1 : Virtual Remote Open Meeting : Schedule 7 of the Approved Fees

b) Phase 2 : Desktop Inspection : Schedule 7 of the Approved Fees

c) Phase 3 : Virtual Remote Inspection : Schedule 7 of the Approved Fees

11. Exemption from the emergencies/disasters including the COVID- 19 pandemic inspection schedule

Generally, a facility/site will not be exempted from the emergencies/disasters including the COVID- 19 pandemic inspection schedule. Sites/ facilities are expected to be operational with office operations not absolutely interrupted by the emergencies/disasters including the COVID- 19 pandemic regulations therefore complying with good practices as determined by the Regulator. However, you may still request exemption in some exceptional circumstances. If you intend to request that we exempt your facility/site from the inspection schedule, you should ensure that you provide the appropriate level of detail and justification upfront via a cover letter submitted with the application and/or an email to SAHPRA.

12. SAHPRA on-site inspection in exceptional circumstances

If the facility/site manufactures one of the product types that was not in the previous SAHPRA/MCC inspection(s) and product is due for registration, or facility/site manufactures sterile (or high risk) products, or the facility/site applied for manufacturing and/or quality control testing SAHPRA license and this included conduct of clinical trials.

You cannot cancel a SAHPRA on-site inspection by appealing the emergencies/disasters including the COVID- 19 pandemic inspection process decision.

Important - SAHPRA has the right to inspect the facility/site regardless of what other evidence you supply—for example, we may as a Regulator:

a) have identified issues during the desktop inspection and/or virtual inspection and
b) have received other regulatory information or have concerns about the facility/site 's level of compliance.

13. Definitions

The definitions provided below apply to words and phrases used in these guidelines. Facilities / sites should also consider the definitions as prescribed by the Medicines and Related Substances Act, 1965 as amended, and the Pharmacy Act, 1974 (Act 53 of 1974).

Applicant.	A person who applies for license in terms of section 22C(1)(b), certificate of registration in terms of section 15, of a medical product to the national regulatory authority, who must be the owner of the product. The applicant may be a manufacturer or the party applying for a product certificate. After the product is registered, the applicant becomes the holder of certificate of registration (HCR).
Pharmaceutical product.	Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.
Quality control.	All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical

	products conform with established specifications for identity, strength, purity and other characteristics.
Quality Management System.	An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.
Quality system.	The sum of all features that are necessary to implement an organization's quality policy and meet quality objectives. It includes organizational structure, responsibilities, procedures, systems, processes and resources. Typically, these features will be addressed in different kinds of documents, such as the quality manual and documented procedures.
Remote Virtual Inspection:	This is Inspection of a facility conducted using information sharing platforms which is agreed upon prior to inspection. At this point SAHPRA is using Microsoft Teams Software.
Covid-19 pandemic:	The COVID-19 pandemic, also known as the coronavirus pandemic, is an ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Responsible Pharmacist:	A natural person who is a Pharmacist and who shall be responsible to the council for complying with all the provisions of this Act and other legislation applicable to services which specially pertain to the scope of practice of a pharmacist, and the legislation applicable to the pharmacy which is under his or her personal supervision;
Desktop inspection:	A review of the requested and submitted documents remotely. This can be in conjunction between SAHPRA and the Company
Principal Investigator:	The person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

GxP: Good Manufacturing Practises, Good Wholesaling Practises, Good Clinical Practises, Good Distribution Practises, Good Laboratory Practises etc. Good Clinical Practice (GCP) : A standard for clinical trials/studies which encompasses the design, conduct, performance, monitoring, termination, auditing, recording, analyses, and reporting and documentation of clinical trials/studies and which ensures that the trials/studies are scientifically and ethically sound and that the

clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented and the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.