AFRICAN MEDICINES REGULATORY HARMONISATION,
AMRH GMP INSPECTIONS

SOPs and Guidelines

Inspector's Playbook

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

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GMP Inspectors Competency Framework

Competence Requirements, Assessment Framework and Training for GMP Inspectors

1. Introduction

This framework defines the competence requirements, assessment framework and training or professional development needs for inspectors specialising in conducting GMP/GLP/GCP inspections on behalf of the African Medicines Agency, AMA. The information and requirements are based on an adaptation of the European Medicines Agency (EMA) competence requirements and training needs for quality evaluators, 2011[1], WHO Inspectors competency framework, the Regulatory Affairs Professional Development Framework, 2013[2], and PICS training for inspectors.
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Key objectives

- Define competence criteria for AMRH GMP inspectors
- Establish a competency assessment framework
- Establish a consistent framework for professional development for GMP inspectors who will conduct GMP inspections on behalf of the AMRH

2. Competency Level of Inspectors:

This competency framework describes the AMRH GMP inspector at three levels: I, II and III. The framework presents the primary basic knowledge, skills/abilities and institutional knowledge requirements for each level.

2.1 Level I – Foundation – Observer Inspector

Pre-requisites

a. Level I inspectors should have appropriate academic background and/or experience, such as university qualification in pharmacy, pharmaceutical sciences, chemistry, medicine, veterinary, biological sciences or relevant fields and understand specific aspects of pharmaceutical manufacturing and the applicable guidelines.

b. A minimum of 1 year of working experience in a relevant field, such as in medicine regulation, pharmaceutical manufacturing industry, research and/or academia, is required.

c. Furthermore, the regulatory inspector should demonstrate good planning, writing, interpersonal and communication skills.

d. A higher academic qualification, such as a master's degree in pharmaceutical sciences or related fields, would be an added advantage.

Expectations & requirements at this level

The inspector will develop essential knowledge and understanding of regulatory and legal frameworks, regulatory requirements, legislation, guidelines, processes and procedures. These individuals focus on hands-on training to strengthen and develop essential skills in areas such as, but not limited to, inspection process and report writing, functions of AMA and the AMRH programme, preparing for inspection, communication and collaboration internally.

Work carried out by individuals in this grade is performed under the supervision of more experienced inspectors. Inspectors with limited experience require significant support and supervision to attain the necessary skills. The regulatory inspectors at this level are encouraged to think for themselves, take responsibility for their work, and develop greater independence.

2.2 Level II – Specialisation level – Co-inspector

The inspector has demonstrated that they are competent to work independently and without supervision and have the necessary technical and organisational skills to inspect different areas of the QMS and facility. Level II inspectors must continue to develop in the job to enable them to inspect complex facilities as their training and competence develops.

The candidate must have completed or passed the Foundation Level.
(Conditional exemptions may be granted based on previous practical experience)

Candidates would have up to 24 months to complete level II based on a defined curriculum, which will cut across inspection planning, inspection of all areas of QMS for general dosage forms facilities and sterile manufacturing facilities and the relevant utilities.

1. European Medicines Agency. Competence requirements, and training needs for quality evaluators, April 2011
2. Regulatory Affairs Professionals Society (RAPS) Professional Development Framework (PD Framework) for the healthcare product regulatory affairs (RA) profession, 2013

Level II inspectors should demonstrate a good understanding of guidelines and high communication, planning, leadership, organisation and time management skills.

2.3 Level III – Advanced Level – Lead Inspector

- Level III consists of more experienced inspectors who are expected to make an advanced contribution to the regulatory sciences and may be recognised as an expert in a particular field based on increased breadth or depth of skills.
- In addition, a Level III inspector should have knowledge and personal skills appropriate to mentoring and developing less experienced staff to enable them to work independently.
- In addition, a Level III inspector should be able to inspect complex facilities and dosage forms, including biological products.
- The inspector should have an up-to-date knowledge of the broader regulatory environment and processes that affect the operations (and, therefore, evaluations) of AMRH.
- Level III inspectors have strong technical and management skills and demonstrate skills and knowledge in areas such as, but not limited to, regulatory strategy and operations, risk assessment and management, monitoring and communicating change in the regulatory environment, global communication, and influencing the regulatory environment.

2.4 General comments

Within each level, the training needed depends on the individual's previous experience; training is therefore customised accordingly. Delegation of work from higher-level inspectors to lower levels is optional. In such cases, the lower-level inspector works under the supervision and responsibility of the higher-level inspectors.

3. Key criteria

The critical criteria to analyse the roles are as follows:

A. **Scientific knowledge and skills** – these are required to achieve the job's overall purpose, gained through education, training and experience (in-house and external).

B. **Regulatory knowledge and experience** - the regulatory knowledge and understanding to achieve the overall purpose of the job gained through training and experience, both internal and external.

C. **Challenge within the role** - the quality of thinking demanded of the jobholder to solve problems and the application of knowledge to identify solutions. Assessment of the degree to which procedural guidelines are available and peer review and support is required.

D. **Decision making/level of responsibility** - the level of scope the role holder has for providing advice and making decisions. The degree of discretion the jobholder has to act, the necessity for work to be checked and signed off and the availability of recommendations from colleagues.

E. **Social skills and attunement to internal and external context** - the nature of communications and the level at which the role holder is required to operate both within the organisation and externally, requiring awareness of assessment context (patient, pharmaceutical company, national and international review situation).

F. **Institutional Knowledge** – the knowledge and understanding of the institutional, legislative mandate, history, philosophy, culture, policies, processes, goals, code of ethics and interdivisional/ departmental relationships.

Profile matrix provides an association of the key criteria progression with increased competency in a cumulative manner. Each level can be compared to this 'matrix' to determine the skill set and competencies required for the evaluator to perform at that level.

The profile matrix provides a framework for assessing competency at each level, identifies expectations of inspectors at each level, and the degree of supervision required and can be used as a development pathway/ tool for evaluators of regulatory inspectors.

3.1 Learning curve

It is important to specify that besides defining the key criteria for the inspector levels and their increasing levels of progression within each job, there is also a clear learning curve/development pathway for inspectors. Levels I to III are defined to make a career development plan possible from one level to the next. The levels can be considered developmental phases

from entry level through intermediate to senior Lead Inspector.

The speed with which an inspector will get to grips with the job at a new level and can move through the learning curve will vary depending on:

- Their aptitude for the work
- The level and relevance of their previous experience and academic qualifications
- The degree of support and training provided

Therefore, a degree of flexibility must be built into the development of regulatory inspector induction/ development programmes to reflect these differences and meet individual needs. In addition, the individual may be developing or have developed either one or more defined areas of expertise or will have a broader understanding across a range of subject areas. So, for each role, the following progression can be envisaged: Learning Zone, Effective Zone and Fully Effective.

3.2 Learning curve implications

The impact of introducing a learning curve concept is seen in the role profile matrix in the creation of 'new entrant' and 'post-induction' profiles within Level I.

Regarding Level II and III, as most appointments are made internally in the GMP TC, if an external candidate is appointed at this level, an induction programme can be developed based on lower-level competence criteria.

The three zones of the learning curve are reflected in the work allocation grids:

a. **The learning zone** relates to the new inspector role. A new inspector will initially concentrate on understanding AMRH's activities and becoming familiar with the key activities and responsibilities of the job.

b. **The effective zone**, which refers to the majority of role holders, indicates that the role holder has gained sufficient experience and is competent to deliver on all the main aspects of the job.

c. **The fully effective zone** is generally where an individual has gained such experience that they not only fulfil the main activities of the role but whose performance in each area is exemplary. Such individuals are also likely to have greater responsibilities, a wider remit and undertake the most complex assessments. They may be working towards becoming an expert in a particular scientific field (depending on the level).

4. Profile Matrices

4.1 Profiling the three levels of Inspectors

Table 1 – Profile Matrix to create a job profile

	Level I	Level II	Level III
Key requirements	*The inspector is at a junior level in their own professional career and inexperienced in the NRA/AMRH activities*	*The individual is established in their own professional career and has demonstrated competence in the key aspects of the job*	*The individual in this role will be expected to make an advanced contribution to the AMRH and may be recognised as an expert in a particular field.*
Scientific experience	▪ Must hold a degree in pharmacy or other relevant scientific discipline. ▪ Limited relevant experience, however must be able to demonstrate a general knowledge of the key scientific activities relevant to the role. ▪ May be new to the AMRH and require an understanding of its key activities.	▪ Must hold a degree in pharmacy or other relevant scientific discipline. ▪ Significant relevant experience is required. ▪ Must demonstrate a broad knowledge across a range of scientific activities or may be beginning to develop a specialist level of knowledge in one or more scientific areas.	▪ Must hold a degree in pharmacy or other relevant scientific discipline. ▪ Has an up-to-date knowledge of a broad range of scientific activities in addition to specialist knowledge in one or more relevant scientific areas. ▪ Is recognised both within the AMRH and by peers outside as an expert/opinion leader.
Regulatory knowledge	▪ They are developing knowledge of regulatory activities. However, they should be able to demonstrate a basic knowledge and understanding of medicines control and regulation.	▪ Must demonstrate a good working knowledge and experience of one or more areas of regulatory activity within the organisation and a broad knowledge of national and global systems and procedures.	▪ Demonstrates a detailed working knowledge and experience of all relevant regulations in one or more areas of regulatory activity within the organisation. ▪ May provide input into developing key regulatory systems policies or definitive guidelines as a recognised expert (both within and outside the organisation). ▪ Provides authoritative leadership in dealing with the most difficult technical or regulatory issues and makes them accessible to others.

	Level I	Level II	Level III
Challenge	▪ Works in a relatively narrowly defined area as may be assigned by the Lead Inspector. ▪ Must meet volume, time and quality targets. Work will be monitored. ▪ Focus on position and function within local organisation; limited role in regional or continental procedures	▪ Work on inspecting a specified section and may work on a range of sections, including more complex cases (e.g. Sterile Manufacturing & Utilities). ▪ Must meet volume, time and quality targets ▪ Challenges are within previous experience, requiring the application of acquired knowledge and experience and the selection of proven solutions. ▪ May act as a peer reviewer/mentor for the work of less experienced colleagues. ▪ Role in regional procedures and organisation under supervision or autonomously. ▪ Represents AMRH at the local level with minimum supervision	▪ Works mainly at their own initiative and effectively inspects the most complex facilities and products. ▪ Either a more broadly defined or a specialist role within the NRA/AMRH. ▪ Challenges are frequently complex, requiring the application of research and newly assimilated knowledge. ▪ Solutions require creative and innovative thinking based on the breadth and depth of knowledge and experience. ▪ Acts as a peer reviewer/ mentor for the work of others. ▪ Participates autonomously in continental/international inspections. ▪ Represents AMRH at regional/ international level.
Decision making	▪ Working to broaden inspection experience, they will seek advice before making routine decisions. ▪ Decisions are guided by standards and practices with limited scope for interpretation and variation.	▪ Identifies key issues and critically evaluates scientific information with minimal support. Will seek advice on decisions outside routine matters. ▪ Makes consistent and reliable judgements on scientific and regulatory issues. ▪ May be required to consult with more experienced colleagues.	▪ Assesses (and/or supports the assessment of) a range of the most sensitive or complex issues. ▪ Coaches others, advises colleagues in their own area of specialisation and provides technical support where required. May act as a mentor to colleagues. ▪ Operates in a supervisory role within the department and provides support to management in the operation of the workstream

	Level I	Level II	Level III
Social skills and attunement	▪ Ability to understand and transfer information on moderately complicated areas. ▪ Ability to prepare general documentation about the role. ▪ Writing skills & communication skills	▪ Successfully transfers knowledge on complicated matters. ▪ Writes inspection reports, briefings or position papers or contributes to guidelines as part of a team and makes effective presentations on scientific/regulatory issues. ▪ Works effectively with external groups (e.g. professional associations) collecting and critically evaluating relevant scientific/ regulatory knowledge.	▪ Writes and critically evaluates written assessment reports and presentations. ▪ Makes individual contributions to other professional or representational activities. ▪ Successfully transfers knowledge on highly complex matters. ▪ Influential in international networks, collects and critically evaluates new and evolving information and influences standards and opinions. ▪ May represent the AMRHs on Scientific/Regulatory policy issues.
Institutional knowledge	▪ Legal mandate of AMRH, history, philosophy, culture, policies, processes, goals, code of ethics, divisional procedures & SOPs, ▪ AMRH information management systems, ▪ Internal communication routes	▪ Legal mandate of AMRH, history, philosophy, culture, policies, processes, goals, code of ethics, divisional procedures & SOPs, ▪ AMRH information management systems, ▪ Internal communication routes ▪ AMRH business/strategic objectives ▪ Training requirements	▪ Legal mandate of AMRHs, history, philosophy, culture, policies, processes, goals, code of ethics, divisional procedures & SOPs, ▪ AMRH information management systems, ▪ Internal communication routes ▪ AMRH business/strategic objectives ▪ Training requirements

4.2 Work allocation per level

Level I Inspector – work allocation

Learning Curve	Objectives/capability	Work assigned	Review/support
Learning zone New inspectors (Up to 6 months)	▪ Completed induction programme. ▪ Familiarisation of work. ▪ Understanding of key processes. ▪ Review and familiarise relevant legal instruments, guidelines, SOP's and standard procedures.	▪ Work categories to be determined against the current skill base and work requirements. If problems occur, they must be raised with a regulatory inspector at Level II or above ▪ Within identified categories: ▪ Less challenging activities (e.g. preparing five questions per section, referencing reports, reviewing responses-CAPA and Investigation reports for defects.) ▪ Dispatching Reports, report writing	All work supervised and/ or monitored
Effective zone (6 – 9 months)	▪ Demonstrates familiarity with standard procedures and processes. ▪ Demonstrates understanding and familiarity with key elements of the job.	▪ Work categories to be determined against the current skill base and work requirements. If problems occur, they must be raised with a regulatory inspector at Level II or above ▪ Within identified categories: ▪ Less challenging activities (e.g. preparing five questions per section, referencing reports, reviewing responses-CAPA and Investigation reports for defects.) ▪ Dispatching Reports, report writing	Appropriate level of supervision to be determined.
Fully effective Up to 12 months	▪ Carries out the full breadth of tasks for the job.	▪ Work categories to be determined against current skill base and work requirements. If problems occur, they must be raised with a regulatory inspector at Level II or above ▪ Within identified categories: ▪ Less challenging activities (e.g. preparing five questions per section, referencing reports, reviewing responses-CAPA and Investigation reports for defects.) ▪ Dispatching reports and report writing.	Appropriate level of supervision (especially for new tasks) and peer review to be determined.

Level II Inspector – work allocation

Learning Curve	Objectives/capability	Work assigned	Review/support
Learning zone (up to 6 months or as required, depending on skill base)	▪ Works independently and takes responsibility for decision-making ▪ To further develop assessment skills set and improve efficiency and understanding of the job requirements	▪ Work assigned by the Lead Inspector based on previous skill base and work allocation. Within identified categories: ▪ Less challenging areas (Inspection of specific sections) ▪ Report writing and referencing from applicable guidelines. ▪	Inspector works independently without close supervision Local peer review procedures are followed with regard to approval of inspection reports
Effective zone	▪ Demonstrates familiarity with standard procedures and processes. ▪ Demonstrates understanding and familiarity with key elements of the job.	▪ General and Sterile Facilities ▪ Inspection of all applicable areas, including utilities and quality control laboratories	Local peer review procedures are followed with regard to approval of Inspection reports May act as a Lead Inspector under the guidance of a Level III inspector
Fully effective	▪ Carries out the full breadth of tasks for the job.	▪ General and sterile facilities ▪ Inspection of all applicable areas, including utilities and quality control laboratories ▪ Participation in regional/continental collaboration activities (if relevant) ▪ Scientific advice to applicants	Local peer review procedures are followed with regard to the approval of inspection reports. Act as a Lead Inspector accompanied by a Level I or II inspector

Level III Inspector – work allocation

Learning Curve	Objectives/capability	Work assigned	Review/support
Fully effective	▪ Demonstrates extensive knowledge of all relevant procedures and processes ▪ Demonstrates complete understanding of the critical elements of the job ▪ Carries out the full breadth of tasks for the job	▪ All types and complexity of inspections and activities	▪ Provides support to colleagues at all levels ▪ Discuss complex issues with the team ▪ Act as a second reviewer for colleagues at all levels ▪ Provides support to management in the operation of the inspectorate.

5. Training

The skill levels, experience and areas of interest of the person assigned to a particular job are compared against the matrix and the work allocation framework to determine where they sit vis-à-vis the job requirements. This forms part of a 'gap analysis'. This process should be carried out upon joining, when appointed to a new job and at regular intervals during the performance evaluation programme (every six months or twice a year).

The matrix and the work allocation framework are useful tools for identifying and developing a training programme for AMRH GMP inspectors at each level (learning zone). Any identified training needs should be considered for inclusion in the training programme for inspectors at each level.

5.1 Training programme

The training manual/programme should be availed for each inspector to support them in fully matching the requirements of an inspector or ensuring their continued development, identifying the nature and type of work that can be assigned to them, and meeting the requirements of the quality system.

5.2 Training process

New inspectors to level 1 should be assessed and mapped against the requirements of an inspector. This should determine the type of work which can be carried out at present and, where appropriate, a rotation programme to ensure they gain exposure to the key areas. Over time, all staff should receive the necessary training and support to meet the requirements of their role. It must be emphasised that the ultimate responsibility for this task rests with inspectorship programme management.

To systematise and document the development of an individual, a process should be put in place that certifies that the necessary training has taken place (every piece of work carried out by an individual as inspector should be appropriately documented).

The key steps of the procedure are:

- A new piece of work is assigned to an individual,
- Guidance/training is provided by more senior inspectors (where appropriate) during the process,
- The individual completes the piece of work,
- Outputs are reviewed and signed off by more senior inspectors in accordance with procedures, which in turn may be countersigned by another management, depending on the nature of the work and the significance of the findings (e.g. potential serious risks to public health),
- Trained/accredited status is awarded on demonstration that the inspector:
    - is capable of completing the work to a suitable quality standard in accordance with the deadline,
    - is aware of the key issues relating to the product,
    - understands the implications/impact of the relevant legislation and guidelines,
    - has gained sufficient practical experience of that type of work by completing a sufficient number and range of activities,
- Depending on the piece of work, 'trained status' may be awarded only on the completion of a number of similar pieces of work.

5.3 Trained/accredited status

Any documentation relating to the awarding of trained/accredited status should be prepared and signed in accordance with AMRH procedures, as appropriate. An individual may attain a trained/accredited status to perform certain pieces of work without supervision, or they may be considered trained/accredited to perform all types of work within the remit of their job. The documentation supporting this may include the following key elements:

- it identifies the individual
- it identifies the trainer
- it determines the type of work as per the technical specifications
- it outlines the steps taken to achieve competency
- a statement from the trainer that the individual has completed the training process
- a statement from the individual that they are now competent to complete this type of work
- a commitment that peer support and guidance will always be available

- a section to be completed by the trainer regarding the effectiveness of the training and recommendations for further training, and degree of support, e.g. continued sign-off or reduction in supervision

Annex 1

Overview of knowledge and skills to be developed in relation to key criteria

Below is a summary of requirements with regard to skills and general and scientific knowledge for inspectors. It is intended to be used in connection with the profile matrix and can be used to define training needs for individual evaluators.

A. General skills required from inspectors: application of scientific skills

Personal characteristics (soft skills):

- Self-dependency
- Efficiency
- Self-organisation
- Ability to follow standardised procedures
- Acceptable interactions with colleagues, etc.
- Ability to attune to relevant internal and external context
- Ability to prioritise work
- Attention to detail
- Ability to estimate risk and identify correlations (logical thinking)
- Ability to communicate clearly with different people

Technical skills:

- Ability to actively apply the concepts of the general GMP guidance, Official monographs if applicable for the specific products, facilities or techniques
- Ability to identify shortcomings/deficiencies and to follow up on issues
- Understanding their shortcomings in knowledge and experience and knows when to ask for advice either from another inspector or from a specific expert, according to the applicable operational procedures
- Basic IT skills (Microsoft Office Suite, internet, email etc.)
- Ability to write clear and comprehensive inspection reports
- Ability to identify relevant and appropriate deficiency points and awareness of the impact /classification
- Sufficient knowledge of written English to express themselves in a concise and clear way

B. Regulatory Knowledge Requirements for AMRH GMP Inspectors

i. Basic knowledge of the legislative system governing the process of approval of medicinal products

ii. Basic knowledge of different dosage forms, e.g. general oral dosage forms, MDIs, sterile products, vaccines, biological, sensitising products, etc.

iii. General knowledge of international and regional regulatory guidance and quality assurance frameworks, e.g. ICH, WHO

iv. General knowledge of AMRH and Expert Committees.

v. The inspector should have sufficient knowledge and understanding of GMP,

C. Basic knowledge requirements for "challenge within role" and "decision making"

Training programmes on basic knowledge of regulatory and scientific guidelines relevant for pharmaceutical assessment should include, but not be limited to, the following topics:

Quality

- General aspects of GMP
- Manufacture of the medicinal product
- Quality Control

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D. Practical Training

It is recommended to include practical training as part of the training programme. If possible, the individual could:

- Maintain a professional development portfolio
- Attend scientific meetings (local, regional and international)
- Participate in external short-term training programmes (e.g. WHO-organised training)
- Participate in internal training programmes
- Participate in GMP inspection
- Participate in relevant postgraduate programmes (e.g. Diplomas/MSc/PhD)
- Participate in accreditation programmes, e.g. Regulatory Affairs Certification (RAC) from Regulatory Affairs Professionals Society (RAPS)

E. Awareness of and attunement to internal and external context & social skills

The individual should be familiar with the decision-making processes at AMRH level and actively contribute to or participate in this process at their specific level in the organisation.

Participation in at least one scientific meeting/ conference (local or international) is recommended

Individuals operating as peer reviewers or coaches of colleagues should have sufficient didactic and social skills, and where relevant managerial skills,

Awareness of social and/or politically relevant topics on product assessments and GMP clearance.

F. Training Map (Curriculum)-Specific Tasks and Outputs

Level I	
Training Areas 1. Training on SOPs 2. Training on inspection techniques 3. Training on legislation applicable to product registration 4. Familiarisation with GMP guidelines 5. Participation in national inspections (3) 6. Participation in international inspections (5) 7. Referencing Reports (5) 8. CAPA Review (5) 9. Report Writing (2) 10. Dispatching Reports (5) 11. Inspection closure (5)	**Output**
Level II	
Training Areas 1. Lead inspection of specific QMS areas-General facility (5) 2. Lead inspection of sterility assurance –Sterile Facility (5) 3. Inspection of Quality control laboratory (5) 4. Inspection of microbiology laboratory (5) 5. Trainee Lead Inspector with level (III)- General Facility (2) 6. Trainee Lead Inspector with level (III)- Sterile Facility (3) 7. Lead inspection with Level II (5) 8. Lead inspection with Level I (5) 9. Train other inspectors (3)	**Output**
Level III	
Training Areas 1. As identified by an inspector or GMP TC	**Output**

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GMP Inspectors Competency and Training Framework

Inspectors Training Manual

Introduction

The training programme aims to equip AMRH GMP inspectors with the necessary knowledge, skills, and techniques to effectively assess pharmaceutical manufacturing facilities and ensure compliance with Good Manufacturing Practice (GMP) standards on behalf of the AMRH. The programme will focus on introductory and advanced GMP topics, including biopharmaceutical inspections, to support the African Medicines Regulatory Harmonisation programme's objective of promoting regulatory convergence and harmonisation across the continent.

The Training manual gives an overview to instructors for the delivery of learning modules on determination of GMP compliance on behalf of the AMRH.

The instructor can be any competent trainer with adequate knowledge of the principles of GMP. The instructor will be expected to deliver the learning modules interactively with learners' engagement and assessment. Specifically, instructors need to:

i. Bridge the skills gap among the learners in GMP,
ii. Articulate the benefits of GMP compliance in support of product marketing authorisation processes and
iii. Emphasise the significance of consistent quality assurance of medicines.

Participants are regulatory staff members of NRAs participating in AMRH. However, other NRAs can also use the same learning materials. The targeted learners are expected to have base knowledge of GMP, including the inspection of various types of manufacturing facilities or knowledge thereof, the different types of published guidelines from the WHO on GMP and the regulation of medicines quality.

Setting

The performance occurs virtually or at physical training workshops. The learners are regulators in countries participating in AMRH, and they can directly apply the learning to their NRAs.

Learners will be nominated by the NRAs or from the expression of interest. They are expected to get support from their supervisors for required learning hours and implement the new knowledge and skills in their jobs. Successful learners will receive a certificate of competence/completion. They will be entered into the pool of competent continental GMP inspectors for eligible selection to perform inspections on behalf of the continent.

Training goals and objectives

Sr. No.	Trainers Manual Description	Inspectors Expectations
1	**Training goal**	To equip AMRH inspectors with skills to perform continental onsite, remote and desk inspections and make informed regulatory decisions on the GMP compliance of sites.
2	**Terminal Objective of the training**	The inspector should perform continental onsite, remote and desk inspections and make informed regulatory decisions on the GMP compliance of sites for use in marketing authorisation processes and lifecycle management.
3	**Performance objective**	To meet the terminal objective, inspectors should, 1. Understand the AMRH programme and processes 2. Understand the AMRH GMP inspection SOPs and guidelines 3. Inspect all areas within a manufacturing facility 4. Assess the documentary evidence and information provided 5. Write comprehensive inspection reports 6. Review CAPAs and determine compliance status 7. Communicate the inspection outcomes
4	**Teaching Strategies**	1. Virtual/physical PowerPoint presentations 2. Group work/case studies 3. Pre-recorded sessions 4. Mock inspections 5. Observed regulatory inspections
5	**Assessment Strategies**	1. Assignments 2. Evaluation tests/quizzes
6	**Overview of the training sessions**	The entire training consists of 7 modules with various sub-topics in each module. Some modules have more content than others. It is not expected that each technical module will take less than one week to complete. All training materials, including PowerPoint slides, reading documents and question banks, should be included in the training folder. At the start of each session, the trainer should take a few seconds to introduce themselves and tell the audience where they come from, their position and their role.
7	**Training schedule and timetable**	1. The total session takes 30 training days to complete 2. All modules must be completed unless exempted by the AMRH secretariat 3. Table 1 below estimates the time the trainers and learners are expected to spend on each session.

Sr. No.	Trainers Manual Description	Inspectors Expectations
8	**Exemptions and waivers**	1. Modules 1 and 2 will be mandatory for all AMRH GMP inspectors. 2. Modules 3, 4 and 5 may be waived partially or in full on merit-based cases, which will include one of the following: a. Demonstrable experience as a Lead Inspector in a WHO PQ, PIC/s, WHO GBT ML3+ NRA inspection for the relevant dosage forms. b. Demonstrable experience as a Co-inspector in a WHO PQ, PIC/s, WHO GBT ML3+ NRA inspection for the relevant dosage forms. The exact contribution to the inspection must be demonstrable to justify a waiver. **All waivers and exemptions to training will be considered on a case-to-case basis by the AMRH secretariat.* ***All eligible for waivers are, however, encouraged to participate in the training as refresher training.*

Training schedule and timetable

Table 1: Summary of activities conducted each session and the estimated time required

Sr. No.	Topic	Activity **Consideration for e-learning pre-recorded sessions*	Time (8-hour days)	Staff responsible
1	**Module 1:** Introduction to the AMRH Initiative	PowerPoint presentation	1	AMRH Secretariat/ Facilitator
2	**Module 2:** AMRH Standard Operating Procedures (SOPs) and Guidelines	Documents (SOPs and guidance documents) presentation	3	AMRH Secretariat/ Facilitator
3	**Module 3:** Introductory Topics to GMP	Pre and post-training quizzes PowerPoint presentations for each GMP topic.	5	Consultant trainers/ Partners/Competent GMP TC members
4	**Module 4:** Advanced GMP Topics	Pre and post-training quizzes PowerPoint presentations for each GMP topic.	5	Consultant trainers/ Partners/Competent GMP TC members
5	**Module 5:** Biological and Vaccines Manufacturing and Inspections	Pre and post-training quizzes PowerPoint presentations for each GMP topic.	5	Consultant trainers/ Partners/Competent GMP TC members
6	**Module 6:** Practical Application and Case Studies	Audit	5	Consultant trainers/ Partners/Competent GMP TC members
7	**Module 7:** Assessment and Certification	Overall test, review and certification of completion	5	AMRH Secretariat
8	**Module 8:** Conclusion and Resources	Review and sharing of resources	1	AMRH Secretariat/ Facilitator
9	**Total time**		**30 training days**	Facilitator

Module 1: Introduction to the AMRH Initiative

1.1 Overview of the AMRH Initiative

1.1.1 Definition and objectives of the AMRH (African Medicines Regulatory Harmonisation) Initiative

1.1.2 Importance of regulatory harmonisation in Africa

1.1.3 Role of GMP (Good Manufacturing Practices) inspectors in supporting the AMRH Initiative

1.2 Key Principles of the AMRH Initiative

1.2.1 Alignment of regulatory standards across African countries

1.2.2 Collaboration among regulatory authorities

1.2.3 Strengthening of regulatory capacity

1.2.4 Harmonisation of inspection practices

1.3 AMRH Initiatives and their Impact on GMP Inspectors

1.3.1 Training and capacity-building programmes

1.3.2 Mutual recognition of inspections and product approvals

1.3.3 Harmonisation of regulatory guidelines

1.3.4 Streamlining regulatory processes

Module 2: AMRH Standard Operating Procedures (SOPs) and Guidelines

2.1 Importance of SOPs and Guidelines in GMP Inspections

2.1.1 Role of SOPs and guidelines in ensuring regulatory compliance

2.1.2 Benefits of following standardised procedures and guidelines

2.2 Understanding SOPs

2.2.1 Definition and purpose of SOPs

2.2.2 Components of an effective SOP

2.2.3 SOP lifecycle management

2.3 Regulatory Guidelines for GMP Inspections

2.3.1 Overview of relevant regulatory guidelines (e.g., WHO, PIC/S, FDA)

2.3.2 Understanding the structure and content of guidelines

2.3.3 Application of guidelines during inspections

2.4 Reviewing and Interpreting SOPs and Guidelines

2.4.1 Techniques for effective review and interpretation

2.4.2 Identifying critical requirements and recommendations

2.4.3 Addressing deviations from SOPs and guidelines

2.5 AMRH SOPs for conducting continental inspections

2.5.1 SOP for scheduling of continental GMP inspections

2.5.2 SOP for preparation of continental GMP inspections

2.5.3 SOP for conducting continental GMP inspections

2.5.4 SOP for continental GMP inspection reporting

2.5.5 SOP for classification of GMP inspection deficiencies and compliance status determination

2.5.6 SOP for review of CAPA and close out of inspections

2.5.7 SOP for tracking of continental GMP inspections

2.6 AMRH guideline and technical guidance documents

2.6.1 AMRH Guideline for GMP inspections

2.6.2 AMRH Guideline for remote/virtual inspections

2.6.3 AMRH guideline for information sharing

Module 3: Introductory Topics to GMP

3.1 Introduction to Good Manufacturing Practices (GMP)

- Definition and principles of GMP
- Importance of GMP in ensuring product quality, safety, and efficacy

- Regulatory requirements for GMP compliance

3.2 GMP Documentation and Records

- General principles for documents and records in the GMP environment
- Essential documents in GMP compliance
    - Batch processing records (BMR & BPR) creation, review, issuance and distribution
    - Test methods, specifications and test results
    - In process checks
    - Line clearance
    - Environmental monitoring
    - Validation protocols and reports
    - Log books/registers
    - Formats, forms and checklists
- Record retention and archiving
- Data integrity in records management

3.3 Facility Design and Maintenance

- Requirements for GMP-compliant facility design
- Critical aspects of facility maintenance and cleaning
- Environmental monitoring and control
- Utilities for facilities
    - Heating ventilation and air conditioning
    - Purified water system and water for injection
    - Gases used in manufacturing
        - Compressed air
        - Nitrogen
        - Qualification of premises
- Preventive maintenance of facilities

3.4 Personnel Training

- Training requirements for GMP personnel

3.5 Personnel Hygiene

- Importance of personal hygiene in GMP operations
- Gowning and personnel flow in controlled environments

3.6 Pharmaceutical Quality System

- Deviation management
- Change control
- Product quality reviews
- Batch release
- Out of specifications
- Quality risk management
- Self-inspections and internal quality audits
- Outsourced activities
- Market complaints
- Product recalls
- Audits, Corrective action and preventive actions

3.7 Good practice in production

3.8 Good practice in Quality control

3.9 Materials management

3.10 Equipment

- Equipment design
- Cleaning of equipment

Module 4: Advanced GMP Topics

4.1 Validation and Qualification

- Principles and importance of validation and qualification
  - Types of validation and qualification activities
  - Validation Master plans
  - Validation protocols and reports
- Considerations for specialised validation of,
  - Production processes,
  - Cleaning methods,
  - Automated systems
  - Analytical methods
  - HVAC

4.2 Sterile products manufacturing

- Environmental monitoring
- Terminal sterilisation
  - Moist air sterilisation
  - Dry heat sterilisation
  - Equipment design and qualification
- Aseptic preparation
  - Requirements for area cleanliness
    - HVAC classification
    - Gowning
    - Personnel behavior
  - Media fill validation
- Sterility testing
  - Design of sterility testing facilities
  - Validation of sterility testing methods

- Lyophilisation

4.3 Emerging trends in pharmaceutical manufacturing

- New technologies
- Continuous manufacturing
- Automated systems

Module 5: Biological and Vaccines Manufacturing and Inspections

5.1 Overview of Biological Products Manufacturing

- Definition and types of biological products, including vaccines
- Importance of quality, safety, and efficacy in biological product manufacturing
- Regulatory framework and requirements for biological products manufacturing

5.2 Manufacturing Processes for Biological Products

- Overview of upstream manufacturing processes
- Overview of downstream manufacturing processes
- Cell culture techniques and fermentation
- Purification methods
- Formulation of biological products
- Aseptic processing and sterile manufacturing

5.3 Quality Control and Testing of Biological Products

- Introduction to quality control principles and procedures
- Analytical methods and testing requirements for biological products
- Stability testing and shelf-life determination
- Release criteria and batch testing

5.4 Vaccine Lot Release

- Sampling procedures
- Testing requirements for safety, quality, and efficacy

- Analytical methods and assays used
- Statistical considerations in lot release

5.5 Adverse Event Reporting and Pharmacovigilance

- Overview of adverse event reporting requirements
- Reporting and investigation of adverse events related to biological and vaccine products
- Pharmacovigilance and post-marketing surveillance

Module 6: Practical Application and Case Studies

6.1 Mock/actual GMP Inspections

- Scheduling and preparation for GMP inspection
- Conducting mock inspections to simulate real-world scenarios
- Identifying potential non-compliance issues
- Developing inspection reports and recommendations
- Classifying deficiencies
- CAPA reviews
- Determining compliance status

6.2 Case Studies in GMP Inspections

- Analysing real-life case studies of GMP inspections using WHOPIRs
- Identifying challenges and lessons learned
- Applying regulatory knowledge and problem-solving skills
- Sharing experiences and insights among participants

Module 7: Assessment and Certification

7.1 Assessment of Knowledge and Skills

- Written examinations to evaluate theoretical knowledge
- Practical assessments of inspection techniques
- Evaluation of critical thinking and decision-making abilities

7.2 Certification of GMP Inspectors

- Criteria and requirements for GMP inspector certification
- Continuous professional development

Module 8: Conclusion and Resources

8.1 Summary and Recapitulation

- Review of key topics covered throughout the training manual
- Emphasising the importance of GMP inspections in supporting the AMRH Initiative

8.2 Additional Resources

- Reference materials, books, and publications on GMP and regulatory affairs
- Websites, online platforms, and databases for regulatory guidelines and updates

8.3 Continuing Education and Development

- Opportunities for further professional development in GMP inspections
- Workshops, conferences, and training programmes available in the field
- Networking and collaboration with regulatory professionals

8.4 Feedback and Evaluation

- Encouraging participants to provide feedback on the training programme
- Evaluating the effectiveness of the training manual and making improvements

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AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

Guidance Document For AMRH GMP Inspections

AMRH Guideline for Good Manufacturing Practice (GMP) Inspections

Disclaimer

Abbreviations and Acronyms

AMRH	African Medicines Regulatory Harmonisation
API	Active Pharmaceutical Ingredient
APQR	Annual Product Quality Review
cGMP	current Good Manufacturing Practices
HVAC	Heating, Ventilation and Air Conditioning
ICH	International Conference on Harmonisation
MRH	Medicines Regulatory Harmonisation
QA	Quality Assurance
QC	Quality Control
RA	Risk Assessment
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
TRS	Technical Report Series
WFI	Water for Injection
WHO	World Health Organisation

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Foreword

This is the first edition of the AMRH GMP guidelines. Generally, AMRH subscribes to the current WHO Good Manufacturing Practice (cGMP) guidelines for inspections of pharmaceutical products. The guidelines were developed and formatted based on the AMRH requirements. The supplementary guidance documents will address issues not explicitly covered in the WHO GMP guidelines mentioned above and serve to clarify the AMRH expectations.

Objectives

- This document has been prepared to serve as a guidance document on the requirements for current Good Manufacturing Practice (cGMP) applicable to the manufacturing of pharmaceutical products. Pharmaceutical products should be manufactured by GMP-approved manufacturers, whose activities are regularly inspected by regulatory authorities.

- This guideline will be used as a standard to attain cGMP compliance, as the AMRH requires. The guide applies to operations for manufacturing pharmaceutical products in their finished dosage forms.

Scope

The guidelines apply to the African member states during the AMRH GMP inspections programme.
The guidance has been drafted to support the registration and marketing of pharmaceutical products in African member states.
It does not create or confer any rights for or on any person and does not operate to bind the African medicine regulatory authorities or the public. The guidance has been drafted to support the legal framework set out in the national legislation in member states.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts ***(adopted from the WHO TRS986 Annex 2).***

Active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Airlock. An enclosed space with two or more doors interposed between two or more rooms, e.g., of differing classes of cleanliness, to control the airflow between those rooms when they need to be entered. An airlock is designed for people, goods and/or equipment use.

Authorised person. The person recognised by the national regulatory authority as responsible for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

Batch (or lot). A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilisation, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. The batch size can be defined as either a fixed quantity or the amount produced in a fixed time interval.

Batch records. All documents associated with manufacturing a batch of bulk product or finished product. They provide a history of each batch of product and all circumstances pertinent to the quality of the final product.

Bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

Calibration. Under specified conditions, the set of operations establishes the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Certification: The final review and formal approval of a validation or re-validation, followed by approval of a process for routine use.

Clean area. An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Contamination. The undesired introduction of impurities of a chemical or microbiological nature, or foreign matter, into or onto a starting material, intermediate or finished product during production, sampling, packaging or repackaging, storage or transport.

Cross-contamination. Contamination of a starting material, intermediate, or finished product with another starting material or product during production.

Critical operation. An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Certificate of analysis (COA). Specification of analytical product tested to confirm the quality of product

Finished product. A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

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

Intermediate product. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Joint inspection. A joint inspection is a procedure in which several NRAs simultaneously inspect the same site to conduct their evaluations in parallel and share their respective scientific evaluations, potentially joining their list of questions or deficiencies to the manufacturer and base their regulatory decision on the outcome of these evaluations.

Manufacture. All operations of purchase of materials and products, production, quality control (QC), release, storage and distribution of pharmaceutical products, and the related controls.

Manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

Marketing authorisation (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognised specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

Master formula. A document or set of documents specifying the starting materials with their quantities and the packaging materials, a description of the procedures and precautions required to produce a specified quantity of a finished product, and the processing instructions, including the in-process controls.

Master batch record. A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Packaging. All operations, including filling and labelling, that a bulk product has to undergo to become a finished product. Filling a sterile product under aseptic conditions or a product intended to be terminally sterilised. It would not ordinarily be regarded as part of packaging.

Packaging material. Any material, including printed material, employed in the packaging of a pharmaceutical, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Production. All operations involved in preparing a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

Qualification. The action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word “validation” is sometimes extended to incorporate the concept of qualification.

Quality unit(s). An organisational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation.

Quarantine. The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

Reconciliation. A comparison between the theoretical quantity and the actual quantity.

Recovery. The introduction of all or part of previous batches (or redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or recovering used materials for a separate use.

Reprocessing. Subjecting all or part of a batch or lot of an in-process medicine, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch or lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological medicines and, in such cases, are validated and pre-approved as part of the marketing authorisation.

Reworking. Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorisation.

Specification. A list of detailed requirements with which the products or materials used or obtained during manufacture must conform. They serve as a basis for quality evaluation.

Standard operating procedure (SOP). An authorised written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning, validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material. A raw material, intermediate, or an API used in the production of an API, which incorporates a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API Starting Materials are typically of defined chemical properties and structure.

Validation. The action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Stringent regulatory authority (SRA)/WHO Listed Authority (WLA)

A National Medicines Regulatory Authority which is strict, precise, and exact with effective and well-functioning systems. Among others, it includes regulatory authorities: Members, observers or associates (before 2015) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Members:

- European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom
- Japan
- United States of America

Observers:

- European Free Trade Association (EFTA) represented by Swissmedic of Switzerland and Health Canada (as may be updated from time to time).
- ***Associates:*** through mutual recognition agreements: Australia, Norway, Iceland and Liechtenstein (as may be updated occasionally).

- For medicines used exclusively outside the ICH region, positive opinions or tentative approval under any of the following three special regulatory schemes are recognised as stringent approval: -

- Article 58 of European Union Regulation (EC) No. 726/2004
- Canada S.C. 2004, c. 23 (Bill C-9) procedure
- United States Food and Drug Agency (FDA) tentative approval (for antiretroviral under the PEPFAR programme)

- A regulatory authority that AMRH has agreed to have an effective and well-functioning medicines regulation system.

- **Where the inspectorate is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)** https://picscheme.org/en/members, the consideration will be made on a case-to-case basis

AMRH member states

Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Djibouti, Egypt, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Republic of Congo, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Mali, South Africa, South Sudan, Tanzania, The Gambia, The Sudan, Togo, Tunisia, Uganda, Zambia, Zimbabwe

AMRH member Regional Economic Communities RECS

1. Economic Community of West African States (ECOWAS)
2. Southern African Development Community (SADC)
3. East African Community (EAC)
4. Intergovernmental Authority on Development (IGAD)
5. Common Market for Eastern and Southern Africa (COMESA)
6. Community of Sahel-Saharan States (CEN-SAD)
7. Arab Maghreb Union (AMU)
8. Economic Community of Central African States (ECCAS)

Harmonised GMP Inspection Process Overview

GMP inspections are conducted in line with current AMRH GMP guidelines by AMRH GMP inspectors chosen from the pool of competent AMRH GMP inspectors. The final GMP inspection reports and compliance/CAPA reports are reviewed virtually (or at the periodic AMRH GMP inspectors' meetings) by the AMRH GMP Technical Committee before they are communicated to manufacturers. The final GMP compliance decision, its validity and communication follow AMRH processes.

The harmonised GMP inspections are conducted for the following reasons:

a. To support the registration of products submitted under the AMRH collaborative registration pathway;
b. To support the approval of variations submitted for additional sites under the AMRH collaborative programme.

Joint inspections may be considered in the following cases;

a. Routine inspections for sites initially approved under the harmonised GMP inspection route
b. Work sharing for common sites among member states
c. Investigative inspections affecting two or more member states

AMRH conducts product line and cost recovery GMP inspections for all manufacturers of pharmaceutical products, vaccines, biological products, devices, APIs and medical products. The inspection fees applicable vary depending on the number of manufacturing blocks, geographical location and the dosage forms marketed in Africa or submitted for registration. The AMRH inspection coordinator generally initiates the inspection process. However, manufacturers may send a formal request or enquiry to the AMRH GMP inspections coordinator. Manufacturers should provide the current Site Master File and list of products marketed or submitted for registration under the collaborative AMRH registration pathway.

NB: It should be noted that member states reserve the right to conduct independent inspections if necessary.

Reliance

AMRH relies on the work done by other regulatory agencies to make risk-informed regulatory decisions. This is done through Desk Reviews of inspection reports from other regulatory Authorities within Africa or Stringent Regulatory Authorities, SRAs and the WHO Pre-qualification programme.

The manufacturer must be willing to share all the required documents for evaluation, including the inspection reports by recognised Authorities, the CAPA, the GMP certificate, APQRs, and the Batch processing records. AMRH, however, reserves the right to determine whether an onsite inspection would be required. All submitted documents will be treated in confidence by all inspectors in accordance with the AMRH Inspectors Code of Conduct. Such information

is usually shared in redacted form. Full information can be shared upon request, where Intellectual Property is preserved.

The application for desk review will be assessed collaboratively by the GMP TC. The outcome/ decision of the desk review process could be approval or recommendation for an onsite inspection. Manufacturers are accordingly expected to send a formal request for a GMP Desk Review to the AMRH GMP Inspections Coordinator

Recognition

AMRH member states will work towards recognition of each other's work.

Setting up of new pharmaceutical manufacturing plants in Africa

Introduction

Setting up pharmaceutical manufacturing plants is a capital-intensive investment and, as such, requires due diligence and compliance from the conceptual design stages. This will ensure that newly constructed plants meet the acceptable cGMP standards. In this context, the AMRH member states are expected to assist committed Greenfield and Brownfield projects by reviewing their plans from conceptual design up to licensing of the plants.

Steps towards licensing of new pharmaceutical manufacturing premises

**This may vary from one NRA to the next. This is just a guide.*

a. Prospective pharmaceutical manufacturers must compile the following documentation and then seek a review meeting with the GMP inspectorate of the member states.

1. Floor plan drawn to scale
2. Personnel flow
3. Process and material flow
4. Spatial surrounding environment
5. HVAC classification zoning schematic diagrams
6. HVAC pressurisation diagram
7. Dust extraction schematic diagram (for oral solid dosage forms).
8. Drainage schematic and Effluent treatment design or description
9. A brief description of the proposed utilities applicable, e.g., HVAC, Water system, Effluent treatment
10. Quality Control laboratory schematic drawing, including the microbiology laboratory, where applicable
11. Technical feasibility study report
12. Detailed description of the design and concepts

*Member states that do not have the institutional capacity to evaluate these documents can reach out to the AMRH for technical assistance

b. The manufacturer will proceed with the procurement and civil works after agreeing with the member states GMP inspectorates. Any changes to the agreed plans must be adequately documented, notified and mutually agreed.

c. After completion of construction and submission of a complete application for a Pharmaceutical manufacturer's licence, a physical onsite inspection will be conducted to verify compliance with the agreed plans and cGMP for non-structural systems, which include a documented quality management system and at least qualification of the areas, major equipment and utilities.

d. After a satisfactory inspection, the site will be licensed as a pharmaceutical manufacturer in the respective AMRH member state. However, this does not translate to mean the site is AMRH-approved.

- Any queries, clarifications, contributions and feedback should be submitted to the Head of Agency of the respective National Medicines Regulatory Agency.

GMP inspection reference guidelines

NB:

1. The AMRH GMP inspection programme will be conducted in line with the current WHO guidelines. However, additional resources, guidelines and literature (e.g., PICS, PDA, ISPE/USFDA/EMA) may be used to elaborate the primary WHO references further.
2. The reference guideline documents listed below are the current WHO guidelines and may be updated from time to time. The list is also non-exhaustive.

	GMP Topic/Area	Reference Guidance Document
1	**GMP main principles**	WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/ TRS1025 Annex 6
2	**Water for Pharmaceutical Use**	WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2. **Short name: WHO TRS No. 970, Annex 2** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/ TRS 1025 Annex 3: Production of water for injection by means other than Distillation and distillation and waterwaste treatment
3	**Heating Ventilation and Air-conditioning, HVAC**	Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organisation, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/ Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organisation, 2018 (WHO Technical Report Series, No. 1019), Annex 8. **Short name: WHO TRS No. 1019** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1019/en/

	GMP Topic/Area	Reference Guidance Document
4	**Good practice in Quality Control**	WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1. **Short name: WHO TRS No. 957, Annex 1** http://www.who.int/medicines/publications/44threport/en/ **Good chromatography practices.** WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025, Annex 4. **Short name: WHO TRS No. 1025, Annex 4**
5	**Pharmaceutical Microbiology**	WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2. **Short name: WHO TRS No. 961, Annex 2** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
6	**Sterile products**	WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6. **Short name: WHO TRS No. 961, Annex 6** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1 PICS guide to good manufacturing practice for medicinal products, Annex 1 (sterile medicinal products) https://picscheme.org/docview/4590
7	**Finished goods transportation validation**	Model guidance for storing and transporting time- and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organisation, 2011 (WHO Technical Report Series, No. 961), Annex 9. **Short name: WHO TRS No. 961, Annex 9** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1 WHO Technical supplements to Model Guidance for storing and transporting time- and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. **Short name: WHO TRS No. 992, Annex 5** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

	GMP Topic/Area	Reference Guidance Document
8	**Quality risk management**	WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. **Short name: WHO TRS No. 981, Annex 2** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/ International Conference on Harmonisation, ICH, Q9 Quality Risk Management https://database.ich.org/sites/default/files/Q9_Guideline.pdf Include the PICS guidance
9	**Non-sterile process validation**	WHO Guidelines on Good Manufacturing Practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organisation, 2015 (WHO Technical Report Series, No. 992), Annex 3. **Short name: WHO TRS No. 992, Annex 3** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
10	**Data integrity**	Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5. **Short name: WHO GDRMP guidance** or **WHO TRS No. 996, Annex 5** http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
11	**Hold time studies**	WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. Short name: WHO TRS No. 992, Annex 4 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
12	**Site Master File**	WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. **Short name: WHO TRS No. 961, Annex 14** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
13	**Sampling**	WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4. **Short name: WHO TRS No. 929, Annex 4** http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

	GMP Topic/Area	Reference Guidance Document
14	**Validation** - HVAC - Water system - Analytical methods - Computerised systems - cleaning - Guideline on qualification of equipment and systems - Non-sterile process validation	WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report (WHO Technical Report Series, No. 1019). **Short name: WHO TRS No. 1019, Annex 3** https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1
15	**Hazardous substances**	WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. **Short name: WHO TRS No. 957, Annex 3** http://www.who.int/medicines/publications/44threport/en/
16	**Chemical reference standards**	General guidelines for the establishment, maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. **Short name: WHO TRS No. 943, Annex 3** http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
17	**Technology transfer**	WHO guidelines on technology transfer in pharmaceutical manufacturing. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7. **Short name: WHO TRS No. 961, Annex 7** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
18	**Biological products**	WHO Expert Committee on Biological Standardization Sixty-sixth report **WHO Technical Report Series, No. 999, 2016) Annex 2** https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1
19	**Blood products**	WHO guidelines on good manufacturing practices for blood establishments, Annex 4; World Health Organization **WHO Technical Report Series, No. 961, 2011** https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1
20	**Stability studies**	WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-second report **WHO Technical Report Series, No. 1010, Annex 10** http://apps.who.int/medicinedocs/documents/s23498en/s23498en.pdf

	GMP Topic/Area	Reference Guidance Document
21	**Herbal medicines**	WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-second report **WHO Technical Report Series, No. 1010, Annex 2** http://apps.who.int/medicinedocs/documents/s23498en/s23498en.pdf
22	**Biosimilars**	WHO Expert Committee on Biological Standardization Sixtieth report; **WHO Technical Report Series, No. 977, 2013 Annex 2** https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1
23	**Pharmacovigilance**	https://www.fda.gov/media/71546/download
24	**New premises**	The manufacturers are free to use any reference engineering texts that help them attain the WHO cGMP Compliance. The following organisation can be used as an example; 1. International Society of Pharmaceutical Engineering https://ispe.org/ The supplementary guidance in this document also assists with establishing acceptable new pharmaceutical plants within the AMRH member states.
25	**Inspection report**	Guidance on good manufacturing practices: inspection report https://cdn.who.int/media/docs/default-source/2021-dha-docs/trs996_annex4.pdf?sfvrsn=c44d141a_1&download=true
26	**Supplementary GMP resources**	1. PIC/S https://picscheme.org/docview/4590 2. European Medicines Agency, EMA (Eudralex Volume 4), Good manufacturing practice, https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en 3. USFDA Current Good Manufacturing Practice, https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations 4. Other non-regulatory GMP resources like ISPE, PDA, etc

Guidance on risk-based classification of deficiencies

Introduction

This document helps ensure consistency among AMRH inspectors during GMP inspections when classifying good manufacturing practices (GMP) observations according to risk. It also informs industry of the situations AMRH considers unacceptable that may result in a non-compliant (NC) rating and/or compliance.

Guidance to assigning risk to an observation

Definitions

Critical deficiency

A critical deficiency may be defined as an observation that has produced or may result in a significant risk of producing a product that is harmful to the user.

Major deficiency

A **major** deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorisation and/or pre-qualification application (including variations);
- indicates a significant deviation from the GMP guidelines;
- indicates a failure to carry out satisfactory procedures for the release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil their duties;
- consists of several other deficiencies, none of which on its own may be major but which, together, may represent a major deficiency and should be explained and reported as such.

Minor/Other deficiency

A deficiency may be classified as **minor/other** if it cannot be classified as either critical or major but indicates a departure from GMP. A deficiency may occur either because it is considered minor or because there is insufficient information to classify it as major or critical. Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances, an example of another deficiency may be categorised as major.

Inspectors will generally consider the following when assigning risk ratings:

- Risk will be assigned in relation to the nature of the product, the nature of the deviation, and the frequency of occurrences.
- Risks may be upgraded/downgraded from one class to the next depending on the evidence supporting the non-conformance, the nature of the deficiency and how critical the observation is to the dosage form.
- When making a Critical observation-or when re-evaluating a Major observation as a Critical observation -inspectors should bring this situation to the attention of the company's senior management.
- All observations should be discussed with the auditee and agreed upon during the inspection. In the event of disagreement, the auditee should be able to defend their position with clear, reputable references on the finding in a CAPA response.
- Recurring observations from previous inspections may be upgraded.

NB: The following are typical GMP non-conformances inspectors may observe during an inspection. It is not intended to be an all-inclusive/ exhaustive list, and inspectors may identify other observations.

*The list is non-exhaustive guidance and classification may vary based on the type of the product, facility evidence at hand and scenario quality risk assessment

GMP System	Critical	Major	Minor/Other
Premises	i. No air filtration system ii. Generalised malfunctioning of the ventilation system(s)- Contamination evident. iii. Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high-risk products such as highly sensitising drugs, biological, hormones, cytotoxic drugs or highly active drugs iv. Design of premises does not allow the logical flow of material and personnel - cross contamination/ mix-up is evident	i. Malfunctioning of the ventilation system could result in possible localised or occasional cross-contamination. ii. Maintenance/periodic verification, such as air filter replacement, and monitoring of pressure differentials not performed. iii. Accessory supplies (steam, air, nitrogen, dust collection, etc.) are not qualified. iv. Heat, Ventilation, Air Conditioning (HVAC) and purified water systems not qualified. v. Temperature and humidity are not controlled or monitored when necessary (for example, storage not in accordance with labelling requirements). vi. DAMRHges (holes, cracks or peeling paint) to walls/ceilings immediately adjacent to or above manufacturing areas or equipment where the product is exposed. vii. Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment. viii. Surface finish (floors, walls and ceilings) that do not permit effective cleaning. ix. Unsealed porous finish in manufacturing areas with evidence of contamination (mildew, mould, powder from previous productions, etc.). x. Insufficient manufacturing space could lead to mix-ups. xi. Physical and electronic quarantine accessible to unauthorised personnel/Physical quarantine area not well marked and/or not adhered to. xii. No separate area/Insufficient precautions to prevent contamination or cross-contamination during raw material sampling. xiii. Doors giving direct access to the exterior from core manufacturing and packaging areas used by personnel xiv. Lack of proper facilities to prevent contamination when moving from lower classification to higher classification areas, for instance, airlocks and change rooms. xv. Lack of proper chemical/biochemical waste disposal infrastructure and procedures	i. Un-screened/Un-trapped floor drains. ii. Outlets for liquids and gases not identified. iii. DAMRHges to surfaces not directly adjacent or above exposed products. iv. Non-production activities performed in production areas. v. Inadequate rest, change, wash-up and toilet facilities. vi. Magnehelic gauges used to monitor pressures in the rooms, not temper sealed after calibration.

GMP System	Critical	Major	Minor/Other
Equipment	i. Equipment used for complex manufacturing operations of critical products is not qualified and has evidence of malfunctioning or lack appropriate monitoring. ii. Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment.	i. Equipment does not operate within its specifications. ii. Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerised systems, is not qualified. iii. Tanks for manufacturing liquids and ointments are not equipped with sanitary clamps. iv. Stored equipment is not protected from contamination. v. Inappropriate equipment for production: surfaces porous/ potentially reactive and non-cleanable/material sheds particles. vi. No covers for tanks, hoppers or similar manufacturing equipment. vii. No inadequate precautions are taken when equipment such as an oven or autoclave contains more than one product (possibility of cross-contamination or mix-ups). viii. Equipment location does not prevent cross-contamination or possible mix-ups for operations performed in the common area. ix. Purified water system not maintained or operated to provide water of adequate quality. x. Leaking gaskets with potential impact on product quality. xi. No calibration programme for automatic, mechanical, electronic or measuring equipment/no records maintained. xii. No preventative maintenance programme for major equipment/no records maintained. xiii. No equipment usage logs. xiv. Inadequate cleaning of equipment with evidence of residue carryover xv. Long campaigns during which contamination accumulates xvi. Risks from machine lubricants xvii. Poor control over metal items – in particular sieves	i. Insufficient distance between equipment and walls to permit cleaning. ii. The base of immovable equipment is not adequately sealed at points of contact. iii. Use of temporary means or devices for repair. iv. Defective or unused equipment not removed or appropriately labelled. v. Minor equipment used for non-critical products not qualified

GMP System	Critical	Major	Minor/Other
Personnel	i. The individual in charge of Quality Control (QC) or production for the fabricator of critical/ high-risk products does not hold a relevant qualification in a science-related field to the work being conducted and does not have sufficient practical experience in their responsibility area.	i. The individual in charge of QC or Production for a manufacturer of a low-risk product does not hold a relevant qualification in a science-related field to the work being conducted and does not have sufficient practical experience in their responsibility area. ii. Delegation of responsibilities for QC or Production to insufficiently qualified persons. iii. Insufficient personnel for QC or Production operations resulting in a high probability of error. iv. Insufficient training for personnel involved in production and QC resulting in related GMP deviations v. Key personnel lack defined job responsibilities.	i. Inadequate training records. ii. Insufficient written training programme
Sanitation & Hygiene	i. Evidence of widespread accumulation of residues/ extraneous matter indicative of inadequate cleaning. ii. Evidence of gross infestation.	i. Sanitation programme not in writing but premises in an acceptable state of cleanliness. ii. No standard operating procedures (SOP) for microbial/ environmental monitoring and no action limits for areas where susceptible non-sterile products are manufactured. iii. Cleaning procedures for production equipment not validated (including analytical methods). iv. Inadequate written health requirements and/or hygiene programme. v. Health requirements and/or hygiene programmes not correctly implemented or followed.	i. Incomplete written sanitation procedure. ii. Incomplete implementation of the written sanitation programme.

GMP System	Critical	Major	Minor/Other
Good Practice In Production	i. No written Master Formula. ii. Master Formula or manufacturing batch document showing gross deviations or significant calculation errors. iii. Evidence of falsification or misrepresentation of manufacturing and packaging orders.	i. Master Formula prepared/verified by unqualified personnel. ii. Lack of or incomplete validation studies/reports for critical manufacturing process (lack of evaluation/approval). iii. Inadequate validation of changeover procedures. iv. Unapproved/undocumented major changes compared to Master Production Documents. v. Deviations from instructions during production are not documented and not approved by QC. vi. Discrepancies in yield or reconciliation following production are not investigated. vii. Line clearance between the production of different products is not covered by SOP or documented. viii. There are no regular checks for measuring devices/no records. ix. Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups. x. Inadequate labelling/storage of rejected materials and products that could generate mix-ups. xi. Upon receipt, bulk and in-process drugs, raw materials and packaging material are not held in quarantine until released by QC. xii. Labels are not adequately controlled. xiii. Production personnel using bulk and in-process drugs, raw material and packaging material without prior authorisation by QC. xiv. Inadequate/inaccurate labelling of bulk/in-process drugs, raw material and packaging material xv. Raw material dispensing is not done by qualified persons, according to an SOP. xvi. Master Formula incomplete or showing inaccuracies in the processing operations. xvii. Changes in batch size not prepared/verified by qualified personnel.	i. Incomplete SOPs for handling materials and products. ii. Access to production areas not restricted to authorised personnel. iii. Inadequate checks for incoming materials. iv. Written procedures incomplete for packaging operations. v. Incomplete recall procedure. vi. There is no agreement between the wholesaler, the importer and the distributor relative to the recall of a drug when the importer or distributor assumes the wholesaler's responsibilities with respect to recalls. vii. Incomplete/inaccurate annual product quality review.

GMP System	Critical	Major	Minor/Other
		xviii. Inaccurate/incomplete information in manufacturing/ packaging batch documents. xix. Although documented, a combination of batches done without QC approval/not covered by SOP. xx. No written procedures for packaging operations. xxi. Non-standard occurrences during packaging not investigated by qualified personnel. xxii. Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, and disposal). xxiii. Inadequate handling of outdated/obsolete packaging material. xxiv. No or inadequate self-inspection programme/Programme does not address all applicable sections of GMPs/Records incomplete or not maintained. xxv. Fabrication, packaging/labelling, and testing operations are carried out at a site not holding a valid manufacturing licence. xxvi. There is no agreement between the contractor, the importer and the distributor covering the fabrication and packaging/ labelling operations. xxvii. Recall: i. i.Absence of recall procedure combined with distribution practices that would not permit an adequate recall (distribution records unavailable or not kept). ii. Improper quarantine and disposal practices that would allow recalled/rejected units to be returned for sale. xxviii. Incomplete validation of content uniformity and blending due to sample size taken xxix. Intermediate and bulk products – holding time not set, justified, or respected.	

GMP System	Critical	Major	Minor/Other
Quality Control Department	i. No person in charge of QC is available on the premises. ii. The quality Control department is not a distinct and independent unit, lacking real decisional power, with evidence that the production department or management often overrules QC decisions.	i. Inadequate facilities, personnel and testing equipment. ii. No authority to enter production areas. iii. No SOPs approved and available for sampling, inspection and testing of materials. iv. Products made available for sale without the approval of the QC department. v. Products released for sale by QC without proper verification of manufacturing and packaging documentation. vi. Master production documents not in compliance with marketing authorisation. vii. Out-of-specification test results, deviations and borderline conformances are not properly investigated and documented, according to an SOP. viii. Raw material/packaging material used in production without prior approval of QC. ix. Reprocessing/Reworking done without prior approval of the QC department. x. Lack of or inadequate system for complaint handling. xi. Returned goods are made available for sale without assessment and/or approval by QC. xii. SOPs covering operations that can affect the quality of a product, such as transportation, storage, etc., are not approved by the QC department/not implemented. xiii. There is inadequate evidence to demonstrate that storage and transportation conditions are appropriate. xiv. Lack of or insufficient change control system. xv. For testing laboratories (in-house or contract), the systems and controls in place for the proper qualification, operation, calibration and maintenance of equipment, standards, solutions, and records keeping do not assure that the results and conclusions generated are accurate, precise and reliable. xvi. Products tested at a site that does not hold a valid GMP licence/certificate are not adequately approved/certified. xvii. Sterility testing not performed in a Grade A environment within a Grade B background or in a Grade A isolator within an appropriate background and limited access to non-essential personnel	i. There is no agreement between the contract laboratory and the establishment covering the testing activities. ii. Investigations of non-conformances not completed in a timely manner.

GMP System	Critical	Major	Minor/Other
Quality Control Raw Material Testing	i. Evidence of falsification or misrepresentation of analytical results. ii. There is no evidence of a testing Certificate of Analysis (COA) available from the supplier/ synthesiser, and no testing done. iii. Use of raw material after the expiration date.	i. Reduced testing programme in place without adequate certification of the vendors/suppliers. ii. Water used in the formulation is not of acceptable quality. iii. Insufficient testing of raw material. iv. Incomplete specifications. v. Specifications not approved by QC. vi. Test methods not validated. vii. Use of raw material after retest date without proper retesting. viii. Multiple lots of the same raw material, comprising one reception, are not considered separate for sampling, testing and release. ix. No SOP for conditions of transportation and storage. x. Certification of brokers or wholesalers is allowed without proper documentation. xi. Lack of adequate SOPs and/or SOPs not followed consistently. For example; i. Inadequate or lack of sampling plan, ii. unrepresentative sample size, iii. lack of microbial testing of primary packaging material.	i. Lots identified for confirmatory testing used in production without QC approval. Incomplete validation of test methods
Packaging Material Testing		i. Reduced testing programme in place without adequate certification of vendors/suppliers. ii. Lack of or insufficient testing of packaging material. iii. Inadequate specifications. iv. Specifications not approved by QC. v. No identity test was done by the packager/labeller after receipt on its premises. vi. Certification of brokers or wholesalers is done without proper documentation.	i. Inadequate procedures of transportation and storage. ii. Inappropriate environment and/ or precautions to prevent contamination of packaging material during sampling.

GMP System	Critical	Major	Minor/Other
Finished Product Testing	i. The finished product is not tested for compliance with applicable specifications by the manufacturer. ii. Evidence of falsification or misrepresentation of testing results/forgery of COA. iii. Non-compliant products made available for sale.	i. Incomplete/inadequate/outdated specifications. ii. Finished product specifications not approved by QC. iii. Incomplete testing. iv. No identity testing upon receipt at the site and/or no periodic complete confirmatory testing. v. Lack of or insufficient validation of test methods. vi. No SOP for conditions of transportation and storage. vii. Use of unique identifier principles not meeting the acceptable options.	i. Inadequate method transfer for a validated analytical method. ii. The method validation report does not specify the revision of the analytical method used during validation.
Documetation	Evidence of falsification or misrepresentation of records	i. Lack of or incomplete Master Production Documents. ii. Unavailability of documentation from suppliers in a timely manner. iii. Lack of or incomplete records of sale. iv. Lack of or incomplete records of complaints regarding the quality of a drug.	i. Incomplete plans and specifications for the manufacturing buildings ii. Insufficient retention time for evidence and records to be maintained. iii. No organisation charts. iv. Incomplete records for the sanitation programme.
Samples		i. Retained samples are not kept for finished products. ii. Failure to submit retained samples when alternative sample retention is granted.	i. Samples of raw materials are not available. ii. Insufficient quantity for finished products or active pharmaceutical ingredients (API). iii. Improper storage conditions.

GMP System	Critical	Major	Minor/Other
Stability	i. No data available to establish the shelf-life of products. ii. Evidence of falsification or misrepresentation of stability data/forgery of COA.	i. Insufficient number of lots to establish shelf-life. ii. Insufficient data to establish shelf-life. iii. No action is taken when data shows that the products do not meet their specifications before expiry. iv. Lack of or inadequate continuing stability programme. v. No stability studies pertaining to changes in manufacturing (formulation)/packaging material. vi. Testing methods not validated. vii. No consideration is given to enrolling worst-case scenarios (for example, reworked/reprocessed lots). viii. Inappropriate storage conditions for stability samples.	i. Stability testing is not performed at the time required by the written programme. ii. Review of stability data not performed in a timely manner.
Sterile Products	i. Lack of or inadequate validation of critical sterilisation cycles. ii. Water for Injection (WFI) systems are not validated with evidence of problems such as microbial/ endotoxin counts not within specifications. iii. No media fills are performed to demonstrate the validity of aseptic filling operations. iv. No environmental controls/No monitoring for viable microorganisms during filling for aseptically filled products. v. Aseptic filling operations continued following unsatisfactory media fill results obtained.	i. Aqueous-based products are not subject to terminal steam sterilisation without proper justification or approval through the marketing authorisation. ii. Inadequate room classification for processing/filling operations. iii. Aseptic manufacturing suites are under negative pressure compared to clean areas (C-D). Clean areas (C-D) under negative pressure to unclassified areas. iv. Insufficient number of samples taken for environmental monitoring/inadequate sampling methods. v. Insufficient environmental controls/Insufficient monitoring for viable microorganisms during filling for aseptically filled products. vi. Disinfectants not qualified or adequately monitored. vii. Premises and equipment not designed or maintained to minimise contamination/generation of particles. viii. Inadequate maintenance of purified water and WFI systems. ix. Inadequate re-validation of purified water and WFI systems after maintenance, upgrading, and out-of-spec trends. x. Inadequate training of personnel. xi. Personnel involved in aseptic filling prior to completing successful media fill. xii. Inadequate gowning practices for clean and aseptic areas.	i. Inadequate control of the maximum number of personnel present in clean and aseptic areas.

GMP System	Critical	Major	Minor/Other
	vi. Inadequate environmental conditions for aseptic operations. vii. Absence of leak test for products sealed through fusion method, for example, ampules	xiii. Inadequate sanitation/disinfection programme. xiv. Inadequate practices/precautions to minimise contamination or prevent mix-ups, xv. Non-validated time lapse between cleaning, sterilisation, and use of components, containers and equipment. xvi. No consideration is given to bioburden prior to sterilisation. xvii. Non-validated time lapse between the start of manufacturing and sterilisation or filtration. xviii. Inadequate programme for media fill. xix. Media capability to grow a broad spectrum of microorganisms has not been demonstrated. xx. Misinterpretation of results for media fills. xxi. Samples for sterility testing are insufficient in number or not representative of the entire production run or from parts of the batch considered most at risk of contamination. xxii. Each steriliser load is not considered a separate lot for sterility testing. xxiii. Purified water is not used as the feed water for the WFI system and the clean steam generator. xxiv. Inadequate testing programme for WFI. xxv. The WFI used for the final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and components are not depyrogenated subsequently. xxvi. Inappropriate environment/controls for crimping following aseptic filling. xxvii. Inadequate inspection for particles and defects. xxviii. Gases are used to purge solutions or blanket products not passed through a sterilising filter. xxix. Inadequate integrity testing of sterilising or vent filters. xxx. Steam used for sterilisation is not monitored to ensure suitable quality	

GMP System	Critical	Major	Minor/Other
Pharmaceutical Quality system	i. There is no existing pharmaceutical quality system and no SOPs or policies on handling OOS, deviations, change management, or market complaints.	i. Inadequate product quality reviews ii. Deviations, market complaints, and OOS are not recorded or adequately investigated. iii. Changes affecting marketing authorisation are not properly documented, notified and authorised. iv. Lack of application of Quality Risk Management principles.	i. Lack of /inadequate periodic trending or review of deviations, incidents, OOS, complaints, water system, changes, and risk assessments.

Key relevant guidance document

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), **Annex 2**
   http://www.who.int/medicines/publications/pharmprep/en/index.html

2. SADC Zazibona GMP guidelines

History

Document History		
Version Number	Date Approved	Reason for Change and Amendments
00		New draft GMP guidance document

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

Guideline for AMRH GMP Reliance and Information Sharing

Appendix 2 to AMRH Good Manufacturing Practice Guidelines: Guidelines on Implementing Reliance and Information-Sharing Mechanisms

Disclaimer

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Introduction

The inspections of sites for GMP compliance following the reliance mechanism utilises a risk-based approach relying on inspections (reports) performed by Recognised Regulatory Authorities (RRAs) for an independent final decision to be made by the AMRH Collaborative Medicines Registration Procedure and individual AMRH Member States (MS). Verification is not a scientific assessment but an administrative process to reach a decision based on the inspection by an RRA. The verification process ensures the product and site(s) for GMP inspections, registration and marketing conform to the product and site(s) as inspected and GMP approved by the RRA.

Informed decisions on the GMP compliance of a manufacturing facility can be made, in certain circumstances, based on the work outcome by another regulatory authority or authorities. Consequently, it is possible for Inspectorates of AMRH MS to identify specific instances where an on-site inspection of a manufacturing facility in an overseas territory is not required because an acceptable level of GMP compliance has been confirmed and assured by another regulatory authority or authorities. Ensuring GMP compliance through desktop assessments (inspection), where appropriate, without undertaking an on-site inspection avoids duplication of work between regulatory authorities, reduces the regulatory burden on manufacturing sites, and allows more efficient and effective deployment of regional inspection resources.

Scope

The guidelines apply to manufacturers and AMRH MS participating in the AMRH GMP inspections programme.

The guidelines provide practical steps and approaches to be implemented for applying reliance mechanisms and sharing of GMP inspection-related information between manufacturers and AMRH MS under the AMRH Collaborative Registration Procedure. It provides manufacturers with guidance on mechanisms that may be used for requesting GMP inspections under the reliance approach and their responsibilities in facilitating information sharing among AMRH MS inspectorates.

The document also provides guidance on high-level principles to share GMP inspection-related information and Market product quality surveillance among AMRH MS inspectorates to guide decision-making at national level.

This guideline covers the sites and products which are under the scope of the AMRH MRH GMP inspections programme. This guideline should be read in conjunction with all relevant current guidelines pertaining to GMP inspections. A separate guideline exists for submitting applications for registration of medicines based on reliance.

Legal basis

The guidance has been drafted to support the legal framework set out in the AMRH. An alternative approach may, therefore, be used if such an approach satisfies the requirements of the applicable statutes and regulations in the member states. The guidelines will apply in all AMRH member states. The marketing authorisation holder's (MAH) responsibility is to ensure that the product information complies with all the relevant requirements for the application.

Manufacturers, through their MAH, if different, are reminded that by expressing interest and applying to participate in the AMRH Collaborative Registration Procedure, they consent to share product and GMP-related information among participating AMRH MS.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Abridged review: A limited independent assessment of specific parts of the dossier or submission for suitability of use under local conditions and regulatory requirements of AMRH member states while relying on prior assessment and inspection outcomes from a recognised regulatory authority (RRA) or World Health Organisation Pre-qualification of Medicines Team (WHO PQTm) to inform the decision.

Desk assessment: The evaluation of documentary evidence by a competent regulatory authority recognised by the national regulatory authority for compliance with the required good practices (good manufacturing practices (GMP), good laboratory practices and good clinical practices) in support of marketing authorisation and other regulatory decisions. Desk assessment may be performed in support of a new marketing authorisation or for routine GMP inspection (including in the frame of specified product(s) life-cycle management as required) ***(adopted from the WHO TRS 1010 Annex 9).***

Dossier: The regulatory submission package submitted to the national regulatory authority as an application for marketing authorisation in line with the applicable country requirements and the AMRH Collaborative Medicines Registration Procedure requirements.

Information sharing: An exchange of data between individuals or entities outside the traditional organisational boundaries to achieve a common goal of better policies and deliver better services. This may mean that one party is disclosing information while the other is collecting the information, or both parties are mutually disclosing and collecting information ***(adopted from the WHO TRS 1010 Annex 9).***

Manufacturer: Any person or legal entity manufacturing a product, packaging, repackaging, labelling and relabelling of pharmaceuticals.

Pharmaceutical Inspection Cooperation Scheme (PIC/S): This is a non-binding, informal cooperative arrangement between regulatory authorities in the field of good manufacturing practices of medical products for human or veterinary use ***(adopted from the WHO TRS 1010 Annex 9).***

Reliance: An act whereby a regulatory authority in one jurisdiction or the Z Collaborative Medicines Registration Procedure may consider or give significant weight to work performed by another regulator or other trusted institution in reaching its own decision.

Recognised Regulatory Authority (RRA)/WHO Listed Authority (WLAs): A well-resourced regulatory authority considered to be functioning at the same level as AMRH MRH GMP programme or as a Stringent Regulatory Authority (SRA) or body in GMP inspections that also agrees to provide outcomes of its GMP inspection reports to applicants/authorisation holders or inspected manufacturers. It also agrees to share these documents with the respective NRAs and the AMRH Collaborative Medicines Registration Procedure. In addition to the countries and regional bodies specifically identified and recognised for reliance on GMP inspections by AMRH MS, the following are considered RRAs for GMP inspections under this guideline:

- Members, observers or associates (prior to 2015) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Members:

  - European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom

  - Japan

  - United States of America

  Observers:

  - European Free Trade Association (EFTA) represented by Swissmedic of Switzerland and Health Canada (as may be updated from time to time).

Associates: through mutual recognition agreements: Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

- WHO Pre-qualification of medicines and vaccines programmes

- For medicines used exclusively outside the ICH region, positive opinions or tentative approval under any of the following three special regulatory schemes are recognised as stringent approval: -

▪ Article 58 of European Union Regulation (EC) No. 726/2004

▪ Canada S.C. 2004, c. 23 (Bill C-9) procedure

▪ United States Food and Drug Agency (FDA) tentative approval (for antiretroviral under the PEPFAR programme)

- A regulatory Authority that AMRH has agreed has an effective and well-functioning medicines regulation system.

- **Where the inspectorate is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)** https://picscheme.org/en/members , the consideration will be made on a case-to-case basis

Reliance on GMP compliance

Manufacturers and MAHs can request the reliance pathway as a registration procedure under the AMRH collaborative registration procedure. This intended registration pathway (Reliance pathway) should be indicated on the letter of application and medicines registration application form.

The following will be considered as key practical enablers of facilitating the implementation of reliance procedures among AMRH MS:

▪ **Transparency** — willingness by manufacturers to submit unredacted inspection reports for obtaining information needed to make an informed regulatory decision by AMRH and individual MS.

▪ **Strengthened expertise and competencies in MS** — for highly innovative products, complex and critical products and manufacturing processes.

▪ **Secure information management platforms/ systems** — Availability of secure platforms and procedures for the exchange and management of non-public information among AMRH MS and with manufacturers.

▪ **Sameness of the product and site** – The manufacturer will ensure that the submitted information for a product under the reliance registration pathway is the same as that of the RRA approved by product and site(s).

▪ **Aligned guidelines** – AMRH MS will continue aligning national GMP-related guidelines with regional (AMRH) ones to facilitate timely decision-making by relying on the inspection's outcome, reports and recommendations of the AMRH MRH GMP inspection programme.

▪ **Confidentiality and trust** – Manufacturers will be assured of continued confidentiality by AMRH and MS with "trade secrets" and proprietary information while granting permission to share the information for reliance purposes in regulatory decision-making. Continued assurance of confidentiality will be based on mutual trust between AMRH MS and manufacturers and trust among AMRH MS as guided by the participation agreements in the collaborative procedure.

▪ **Participatory** – AMRH MS will be encouraged to continue participating (actively as work-sharing or passively as an observer) in the technical reviews and discussions of GMP inspection outcomes and reports. This will promote "ownership" of the recommendations of the AMRH MRH GMP inspections programme by MS for effective and efficient decision-making at national levels.

The following will provide specific guidance to MAHs and AMRH MRH GMP inspections programme for considerations under the reliance pathway for site GMP compliance:

	GMP Topic/Area	Reference Guidance Document
1	**Application requirements**	Expression of Interest and application forms for reliance pathway (AMRH collaborative registration procedure). Accessible from the AMRH secretariat.
2	**High-level principles and recommendations for reliance among AMRH MS**	Good reliance practices in regulatory decision-making: high-level principles and recommendations, WHO Expert Committee on Specifications for Pharmaceutical Preparations, TRS1033 section 9.3.1 https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations **if a new version is published, it will replace the preceding reference*
3	**Technical information and dossier requirements for consideration under reliance and collaborative registration pathway among AMRH MS**	Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third report. World Health Organisation, 2019 (WHO Technical Report Series, No. 1019), Annex 6. https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex6.pdf **if a new version is published, it will replace the preceding reference*
4	**Guidance on establishing and implementing reliance mechanisms for GMP inspections**	GMP Inspection Reliance, Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Cooperation Scheme (PIC/S), June 2018. https://www.picscheme.org/en/publications?tri=all **if a new version is published, it will replace the preceding reference*
5	**GMP desk assessment (technical and admin) requirements and methodologies**	Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second report Geneva, World Health Organisation, 2018 (WHO Technical Report Series, No. 1010), Annex 9

A letter of access (annexed to the registration reliance guideline) authorises the AMRH to use the GMP inspection reports of the RRA and/or to contact the specified RRA to obtain reliance documentation for the product and its related sites of manufacture. Reliance documentation includes but is not limited to the complete, un-redacted assessment/evaluation reports, inspection outcomes/reports and laboratory testing results. Where full/un-redacted assessment reports cannot be obtained by the applicant from the RRA, the letter of access will allow AMRH Collaborative Medicines Registration Procedure to request un-redacted reports from the associated RRA(s). However, there is no guarantee that such reports will be obtained.

Even the best/well-resourced NRAs are subject to limitations in terms of time, funding and personnel. Therefore, it is regulatory best practice to apply quality risk management principles in prioritising inspection activities. The desk assessment process should aim to provide to the AMRH MRH GMP programme, in a timely manner, the required assurance that the site(s) in question demonstrates an acceptable level of GMP for the FPPs and APIs. The assessment should consider and focus on the critical products and critical processes in the manufacture of a specified product in relation to patient risk, based on the knowledge that other competent and trusted inspectorates of RRAs have inspected and approved the site of manufacture. Key factors to consider include the origin of the information and its authenticity, the location of the site of manufacture, the complexity and type of the product (whether sterile or biological) and the risk to the patient. To ensure that the desk assessment is effectively and efficiently done, the manufacturer must be willing to share all the required documents for assessment, including:

- Inspection reports relating to the latest (2 years or less) inspections by RRAs with dates when the RRA was on site, inspection scope and outcome, GMP certificate, related company response/corrective and preventative action (CAPA) plan, Annual Product Quality Reviews, batch processing records and planned re-inspection date(s) (if known);
- Post-inspection information provided by the RRA;
- Information relating to inspections by other regulatory authorities in a defined period (e.g. previous 2-3 years or since the last inspection by any of AMRH MRH actively participating MS). For example, the name of the regulatory authority, dates on-site, inspection scope and outcome, and planned re-inspection date (if known/applicable). Inspection reports and company responses could also be requested, as appropriate;
- Site master file (typically, this will be in the WHO format as per AMRH GMP guidelines); and
- Information to aid in an assessment of risk. For example, changes since the last inspection by the RRA to key site personnel or personnel numbers, company ownership, and manufacturing processes and products (e.g. changes in the types or numbers of products manufactured/handled, previously outsourced activities that have been brought back in-house).

Please note that certification or approval of GMP by RRA does not guarantee a site will be deemed GMP compliant by the AMRH MRH GMP programme. AMRH and its individual MS reserve the right to request additional documentation, schedule an inspection or reject any sites regardless of compliance with the following requirements:

- The RRA has approved the site;
- The RRA approved the site within the previous two years;
- The dosage form of the product within the application is similar to the one approved by the RRA;
- The product type applied for is the same as the one approved by the RRA, and
- The activities applied for by the applicant are the same as the ones approved by the RRA.

Information sharing

An application cover letter **(annex 1)** submitted by MAHs or their representatives for the AMRH collaborative registration procedure gives consent to AMRH to share the product information, including GMP inspection information, among all AMRH participating MS.
AMRH MS, who are members of PIC/S, may share GMP inspection information as described in the PIC/S reliance guidance and other related technical guidance documents.

AMRH will encourage MS to continue implementing procedures for publishing GMP inspection reports within the national legislation on intellectual property protection and confidentiality. This approach will improve transparency and facilitate ease of access to

GMP inspection-related information among MS.

GMP inspection information, including previous inspection reports by AMRH MS, company responses and CAPAs, site GMP status, complaints and non-conformances, may be shared among participating MS through established and implemented electronic information management systems for AMRH MS under the AMRH collaborative registration process.

All external and/or consulting experts conducting GMP inspections for AMRH must sign confidentiality agreements accordingly. Information sharing with external experts will be through secure platforms as applicable to ensure information security and integrity. Sharing of information among AMRH MS will be guided by the implemented information management systems (IMS) with requirements for access control and data protection as appropriate. The information will be un-redacted in any way to assist in verifying the sameness of information for the same products and sites to facilitate reliance and work-sharing within AMRH.

To control access and data protection, heads of agencies for each NRA must sign agreements to share information among MS. The agreement will also include nominating one other staff member (or more) who should be granted appropriate rights to upload, change, download and manage the database. Other users will be given access to the database as read-only.

Under GMP inspections, NRAs will also share information on the outcome of the inspections through unredacted inspection reports with accompanying CAPAs, if applicable. This information will be shared to ensure that other AMRH MS know the facility's status in case they have registered products or are evaluating applications for MAH for products from the concerned facility.

In addition to GMP inspection-related information, AMRH MS may use the established network based on work-sharing to share product and site-related information during the pre-registration (pre-approval) and post-marketing stages. This information may be useful for consideration by MS and AMRH in planning and conducting GMP inspections.

The following, but not exhaustive, information will be shared among MS using appropriate and secure information management systems:

- Approved variations by MS and RRAs (for products registered under the reliance pathway)
- Out of specifications (OOS) from routine and targeted post-marketing surveillance (including pharmacovigilance) activities
- Falsified and substandard products
- Complaints and product recalls
- Withdrawal or de-registration of product(s) registered under the AMRH collaborative registration procedure
- Any other information that may require attention or be useful for site GMP status/compliance verification by AMRH MRH GMP inspection programme

AMRH MS will also use the information management system to share GMP training, experiences and other capacity-building information to strengthen national and regional expertise and competencies.

Annex 1: Cover letter - Application for registration of product under AMRH

Applicants Address

Generic name of product, strength and dosage form:
Proposed Trade name:

(Insert name of applicant) hereby submits our application for registration of (insert Generic name, strength and dosage form of product) to be considered under the AMRH collaborative registration procedure in response to the (insert number of applicable EoI, e.g. 1st) Expression of Interest to register medicinal products via the AMRH collaborative process.

We hereby confirm that we are interested in the Authority managing the application in line with the principles of AMRH.

We also confirm our agreement to consent to sharing product-related information among all AMRH authorities during the registration process and post-registration.

We also confirm that the same application is being submitted concurrently to the following countries
1.
2.
3.

I, the undersigned, hereby declare that all the information contained herein and in the appendices is true, complete and correct.

Full Name and Title of Applicant's Representative
Title or Responsibility
Signature of applicant representative

Date

Key relevant reference documents

1. World Health Organisation. Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products, WHO TRS 1019, Annex 6
   https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex6.pdf

2. SA Guide to Good Manufacturing Practice for Medicines, SAHPRA, July 2019.
   https://www.sahpra.org.sa/guidelines/

3. MCAZ Good Manufacturing Practice Guideline, MCAZ, December 2019.
   https://www.mcaz.co.zw/index.php/how-we-regulate/licensing-enforcement/inspections

4. GMP Inspection Reliance, Pharmaceutical Inspection Convention/Pharmaceutical Inspection Cooperation Scheme (PIC/S), June 2018.
   https://www.picscheme.org/en/publications?tri=all

5. Good reliance practices in regulatory decision-making: high-level principles and recommendations, WHO Expert Committee on Specifications for Pharmaceutical Preparations, TRS1033 section 9.3.1
   https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

6. SADC Guideline for GMP reliance and information sharing

Revision history

Document History		
Version Number	Date Approved	Reason for Change and Amendments
01		New draft version

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for Scheduling of Remote-Virtual GMP Inspections

African Medicines Regulatory Harmonisation Guidance Document on Remote-Virtual Good Manufacturing Practice (GMP) Inspections During Emergencies and Special Restrictive Events

Disclaimer

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Special thanks are also extended to the esteemed stakeholders who gave commendable and constructive inputs to improve the document.

Foreword

This is the first edition of the AMRH guidance document. Generally, AMRH subscribes to the WHO current Good Manufacturing Practice (cGMP) guidelines for inspections of pharmaceutical products. AMRH Member States (MS) reserve the right to adopt and adapt other best practices and current guidance from among the MS, African regional harmonisation initiatives (e.g. East African Community – EAC), other SRAs, the European Union through the European Medicines Agency (EMA) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). This guidance document was developed and formatted based on the recommendations and requirements of WHO, AMRH MS, EAC, SRAs, EMA and PIC/S.

Introduction

With the complexity of the supply chains of pharmaceutical products, the demand for inspecting facilities far exceeds what any national or regional regulatory authority can accomplish during emergencies/disasters and other special events, including the COVID-19 pandemic. A framework is required to assist inspectors and AMRH MS in managing GMP compliance risks posed by the increasingly complex pharmaceuticals global supply chain.

GMP inspections are conducted for product registration and to ensure continuous distribution of quality-assured pharmaceutical products. An informed decision on the GMP compliance of manufacturing of APIs and FPPs can be made, in particular (exceptional) circumstances, based on the outcome of virtual or remote inspection by the Regulatory Authority or Authorities.

During emergencies, including the COVID-19 pandemic, on-site inspections may not be possible due to multiple factors such as difficulties and restrictions related to travelling between and within the borders of countries (including travel warnings/restrictions, border controls, transportation difficulties), restrictions to accessing facilities justified by health hazards and local authorities' recommendations/orders, as well as additional health risks for inspectors and manufacturers.

The AMRH harmonised inspections coordinating team, in agreement with the MS requesting the inspection, should make a case-by-case decision based on the eligibility criteria under the scope on whether a remote inspection will be considered appropriate and feasible. Remote or virtual inspections should follow the existing applicable procedures for planning, coordinating, preparing and conducting harmonised GMP inspections. Still, they should also consider the limitations imposed by using a remote process and recognise that such a remote process cannot wholly replace on-site GCP inspections.

This document aims to outline the requirements and specificities of remote harmonised GMP inspections, identifying the points to be considered during the preparation, conduct, and reporting phase in the context of emergencies and other special events, including the COVID-19 pandemic.

This document should be read in conjunction with the AMRH Guidelines on Good Manufacturing Practice and related technical guidance documents.

Purpose

The objective of this document is to guide holders of marketing authorisations, manufacturers, distributors, sponsors and other stakeholders on the requirements for GMP inspections during emergencies/disasters, including the COVID-19 pandemic within AMRH MS. The document focuses on the GMP evidence and the regulatory requirements for manufacturing for current and prospective MAHs in AMRH MS.

Scope

The guidance applies to active AMRH MS NMRAs, MAHs, manufacturers, distributors and sponsors of pharmaceutical products for registration and marketing in the AMRH MS subject to GMP inspections.

In the context of this guidance document, a remote/ virtual GMP inspection is defined as “the process of conducting inspections at a distance/virtually, supported by technology for communicating, sharing, reviewing documents and accessing systems without the inspectors being physically present at the sites where the activities subject to an inspection have taken place /where the inspection would routinely be hosted.” This guidance document uses the terms ‘remote inspection’ and ‘virtual inspection’ inter-changeably.

This definition will include an inspection 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 an internet cloud system when the size of documents cannot be transferred by direct mails (e.g. WeTransfer, Dropbox, Mimecast). Review of documents can also be done within a web-based documentation system.

Remote/virtual GMP inspections will be considered deviations from the AMRH quality system for regular on-site inspections. As a result, the following will be used in determining (case-by-case) the eligibility of a manufacturing site that can be considered for remote/ virtual GMP inspection:

- Travel restrictions between the AMRH MS and the host country of the manufacturing site
- Criticality of the continuity or commencement of supply of the pharmaceutical product to AMRH MS
- Security and integrity of the supply chain of the pharmaceutical product
- Compliance status and history of the site to AMRH MS, SRAs, WHO prequalification, and other recognised regulatory GMP requirements/ standards
- Nature, type and complexity of the manufacturing and quality control facilities (Non-sterile vs sterile facility)
- Nature, type and complexity of the pharmaceutical product (general pharmaceutical products vs. biological/biotechnological products)
- Ability and commitment of the manufacturing site to maintain the technical requirements of the remote/ virtual inspection
- Time-zone differences between the manufacturing site and the inspectors.
- Health and well-being of personnel involved in the inspection
- Other product quality and supply chain-related risks

The AMRH harmonised inspections coordinating team will be responsible, in consultation with MS, for using appropriate risk assessment tools to establish the eligibility of manufacturing sites for remote GMP inspections. For sites considered ineligible for remote inspections but their continued or commencement of supply is critical, the inspections coordinating team will recommend, among others, appropriate alternatives, including relying on the host NRA to conduct the GMP inspection or exceptional travel.

This guidance is not intended for use in or to replace on-site inspections outside of crisis situations.

The guidance document has been drafted to support the legal framework set out in the national legislation in member states.

AMRH member states *(actively participative in the AMRH Medicines Regulatory Harmonisation initiative)*

Evolving list, refer to https://amrh.nepad.org/amrh-countries

Harmonised GMP Inspection Process Overview

Typically, GMP inspections are conducted in line with current WHO GMP guidelines by inspectors from the AMRH pool of competent inspectors. The GMP TC reviews the final GMP inspection reports and compliance/CAPA reports before they are communicated to manufacturers. The final GMP compliance decision, its validity and communication follow AMRH processes.

The harmonised GMP inspections are conducted for the following reasons:

a. To support the registration of products submitted under the collaborative registration pathway;
b. To support the approval of variations submitted for additional sites

Harmonised inspections may be considered in the following cases;

a. Routine inspections for sites initially approved under the harmonised GMP inspection route

b. Work sharing for common sites among member states

c. Investigative inspections affecting two or more member states

AMRH conducts product line inspections for all manufacturers. The inspection fees applicable vary depending on the number of manufacturing blocks and the dosage forms marketed in AMRH MS or submitted for registration. The AMRH inspection coordinator generally initiates the inspection process. Manufacturers should provide the current Site Master File and list of products marketed or submitted for registration under the collaborative AMRH registration pathway.

NB: It should be noted that member states reserve the right to conduct independent inspections if necessary.

Planning/Feasibility Assessment

Remote inspections can be in the form of any of the following types of inspections as necessary:

- Pre-approval inspections (new sites or sites where the current GMP certificate is not valid for the proposed type of product or activity).
- Routine inspections.
- For-cause and investigative inspections.

Remote inspections can be performed for all types of sites and dosage forms following a case-by-case eligibility evaluation through risk-based criteria.

Following a decision to perform a remote inspection, at least one week before the inspection, early contact should be made with the intended site of inspection to determine the feasibility and logistical support needed. Although it is envisaged that manufacturers, importers, and distributors generally have the necessary resources and IT capabilities to support remote inspections, there are a number of practical items that require consideration to determine the scope of the remote inspection and to ensure it is a suitable means of assessing the required areas to allow for a decision to be made regarding GMP compliance. At a minimum, the following items should be considered:

- The use of appropriate platforms to allow for the timely provision of data, such as large electronic documents (e.g. access to secure cloud servers).
- The use of teleconference/videoconference or alternative to allow for real-time discussions with company personnel and Subject Matter Experts (SMEs).
- The capability for the live sharing of screens displaying computerised systems used at the site or the feasibility of providing remote (read-only) access to inspectors to computerised systems.
- The provision of live camera footage or video recordings (e.g. smart glasses, mobile cameras, drones or cameras in place) to allow for a remote review of manufacturing operations, equipment, facilities and relevant documentation such as logbooks, if applicable.
- The time zones of the inspection site and the inspector(s) location.
- The language of the site of inspection. The inspector(s) may require access to a translator for parts of or all of the remote inspection.

A confidentiality agreement will be implemented for the following considerations:

- The realisation of a remote inspection does need to exchange documents, data, videos and photographs through internet-based virtual support software. Therefore, both the inspectors and the site will accept to share information for the inspection only and
- There should be a prior commitment to keep confidential information shared before and during the audit and to make the auditee aware of the storage and archiving of any photographs, videos or documents provided by the auditee.

The outcome of these considerations may highlight whether the inspection site or the inspectorate(s) conducting the inspection require additional resources. It is preferable that the company host and manage the communication platform and consider its security requirements. In cases where the company does not have or cannot obtain the appropriate capabilities, the inspectorate(s) could consider hosting the communication platform.

An example of an optimal communication platform could include the following:

- A live videoconference platform which has the following capabilities:
  - Break-out rooms/conferences to facilitate separate channels of discussion between different members of the inspection team and the company.
  - Screen sharing to display company applications/ electronic systems.
- Smart glasses or other mobile cameras can be interfaced with the videoconference platform to provide live footage of manufacturing operations, facilities and equipment.
- Access to a secure cloud server to share documents.

The practicalities and potential challenges associated with remote inspections should also be considered and could result in a longer duration than an equivalent on-site inspection. Aspects such as the communication

process, company time zone and language, and location(s) of the inspection team should be taken into account.

Planning and preparation

Procedures and communication for planning and preparation of remote/virtual inspections will be performed the same way as on-site inspections once eligibility of the site has been confirmed.

The inspector(s) should prepare adequately for the remote inspection and familiarise themselves with the company to be inspected, per the relevant AMRH GMP procedures and quality systems.

It is recommended that an inspection plan be drafted in a manner similar to on-site inspections, outlining the areas of the site to be reviewed by each inspection team member. It is also recommended to share relevant parts of the inspection plan and timetable with the company to facilitate the smooth running of the inspection and ensure that company SMEs are available at the requested times.

Notification of the intention to perform a remote inspection should be communicated to the company in accordance with the standard timelines for on-site inspections. To prevent any delays during the inspection, consideration should be given to requesting that electronic copies of documents and/or lists of documents be provided to the inspector before the inspection or, at least, are available for review from the start of the inspection.

The company should be requested to provide the following GMP-related documents, preferably in PDF or equivalent searchable format, to enable the inspection preparation by the inspection team:

- quality manual,
- Site Master File
- Site floor layouts
- master list of procedures and all key SOPs,
- master validation plan (MVP),

This list should include all documents usually reviewed before an on-site inspection, depending on the site type (e.g. FPP site or API site). The documents should be sent approximately one week for review by inspectors before the scheduled start of the inspection.

The communication platform and process for providing electronic copies of documents and other information to the inspector(s) should be defined and agreed upon with the company before the remote inspection.

If there are significant differences in the time zones of the inspector(s) and the company, company personnel may not always be available to respond to inspector queries in real-time. In such cases, the inspector(s) should ensure that they have sufficient documentation available for review when company personnel are not online, and related queries should be logged as documents are being reviewed. In these circumstances, efforts should be made to ensure that there is at least a sufficient overlap time each day to hold discussions in real-time.

The communication process between inspectors should also be determined if inspectors are based in different locations. To avoid duplication of review or document requests, consideration should be given to making all requests for documents and other information visible to all inspection team members.

It is recommended that the communication platform is tested before the commencement of the inspection to verify its functionality. If possible, IT support staff should be readily available to respond to any IT issues that may arise during the remote inspection. The company should also be aware that if there are any unexpected delays in providing electronic copies of documents to the inspector during the inspection, the inspector(s) should be informed immediately. Creating a WhatsApp group for everyone involved in the inspection is recommended.

Conduct of the inspection

The inspection should start with an opening meeting via videoconference, teleconference or alternative. In addition to the procedures for on-site inspection during the opening meeting, inspectors should consider outlining the following:

- A brief overview of the process for communication and the inspection plan/timetable.
- Any video/audio recording of the remote inspection should be agreed between the company and the inspector(s). If part of the inspection will be recorded, the company should be allowed to appropriately inform any personnel who may appear in such video footage in accordance with any relevant local legislation.

The manufacturer should ensure that representatives for each topic and each function are available. Therefore, the continuous communication between inspectors and the manufacturer's team leader is crucial for adapting the agenda continuously.

Submissions of the requested documents in the inspection for each site should be submitted or access granted to a web-based documentation system by the Head of Quality Assurance or equivalent personnel.

Remote/virtual inspections will involve a detailed evaluation of the specified documentary evidence supplied by the site/facility against GMP guidelines and regulations as determined by the inspectors.

Documents to be submitted as evidence of compliance with GMP 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 be 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 GMP compliance will be determined.

Relevant elements of the AMRH harmonised inspection procedures should be considered to assess compliance with GMP and the terms and conditions of authorisation(s) as applicable.

If an inspection of manufacturing operations, facilities and equipment is facilitated through the use of cameras or video footage, it may be helpful to have the site schematics, drawings and/or process flow diagrams available for reference as relevant. This may help the inspector(s) orientation during the virtual tour.

To facilitate the smooth running of the inspection, at the end of each day, the inspector may consider informing the company of the documentation intended to be reviewed the following day to give sufficient notice for the scanning and provision of the requested documents. As the inspector reviews a new topic (e.g., deviations, process validation, etc.), promptly communicating this to the company may also be helpful.

Inspectors should record notes on the documents being reviewed as per on-site inspections. Relevant documents, e-mails and other information received should be securely saved or deleted as required.

The inspection should end with a closing meeting via videoconference, teleconference or alternative. It should cover the relevant items listed in the closing meeting procedures for on-site inspections.

Post inspection activities

Inspection reports are written in line with the AMRH formats of GMP on-site inspection reports. Appropriate clarifying remarks should be included in relevant sections of the report to make it clear that the inspection, or part of the inspection, was remote and to indicate if the physical aspects of the facility were assessed and what methods were used.

If the outcome of the remote inspection and CAPA review is positive, GMP certificates/approval should be issued by the AMRH. The *Type of Inspection* on the certificate should indicate *virtual/remote inspection*. If part of the inspection consists of a limited on-site inspection, the *Type of Inspection* on the certificate should reflect the on-site inspection, and a clarifying remark may be included to indicate that part of the inspection was performed remotely.

Existing regulatory risk management principles and AMRH policy should be used to determine the duration of the validity of GMP certificates/approvals issued following remote inspections.

For new sites, including sites inspected in a pre-approval GMP inspection, if any critical deficiencies are identified during the remote inspection, the relevant application should be put on hold until an on-site inspection can be performed.

For other types of inspections, if any critical deficiencies are identified during the remote inspection, existing processes for on-site inspections should be followed, and a Statement of non-compliance may be issued if applicable.

A remote inspection may be a suitable justification to recommend a reduced interval until the next on-site inspection. The following items could also be taken into consideration:

- The risk and complexity of the dosage form/active substance/manufacturing process.
- The compliance history.
- The type of remote inspection (e.g. for-cause inspections or inspections to support an assessment of a new kind of product or activity).

Generally, a facility/site will not be exempted from emergencies/disasters, including the COVID- 19 pandemic inspection schedule. Sites/facilities are expected to be operational with office operations not completely interrupted by emergencies/disasters, including the COVID-19 pandemic regulations, therefore complying with good practices as determined by the regulators. However, sites may still request exemption in some exceptional circumstances. Suppose sites intend to request an exemption from the inspection schedule. In that case, sites should provide the appropriate detail and justification upfront via a cover letter submitted with the application and/or an e-mail to AMRH.

Key references

1. Guidance on good practice (GXP) inspections during emergencies/disasters, including the COVID-19 pandemic, South African Health Products Regulatory Authority, June 2020

2. Guidance on remote GCP inspections during the COVID-19 pandemic, European Medicines Agency, May 2020

3. MCAZ Remote inspection guidelines

Revision history

Document History		
Version Number	Date Approved	Reason for Change and Amendments
01		New SOP

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for Scheduling of GMP Inspections

1. Policy

Inspections must be scheduled such that they are conducted in the most efficient manner possible. This involves combining facilities within a schedule to ensure efficient cost recovery.
Scheduling should, as far as possible, support the assessment sessions with a verdict on the GMP status of the manufacturing sites for products under consideration. The AMRH GMP Steering Committee will set the annual targets for inspections.

2. Scope

This procedure applies to scheduling inspections for manufacturers of finished pharmaceutical products (FPP), contract research organisations (CROs), and quality control laboratories to be inspected under the AMRH collaboration. It provides guidance on compiling an inspection schedule, the composition of an inspection team and the duration of inspections.

3. Purpose

This SOP ensures that GMP, GCP and GLP inspection scheduling follows a standardised procedure. Effective implementation of the SOP should ensure that adequate resources are planned for and made available for the inspections.

4. Definitions

i. AMRH Inspections coordinator- a member of the Secretariat assigned to carry out the roles of coordinating the continental inspections and inspection activities.

ii. AMRH – African Medicines Regulatory Harmonisation. This term will be replaced with African Medicines Agency once it becomes operational.

5. Responsibility

i. AMRH Inspections Coordinator

- scheduling of inspections
- Initial communication with sites to be inspected for scheduling

ii. AMRH secretariat

- provision of resources (per diems, air tickets and other requirements needed to make the travel) to carry the inspection

6. Procedure

a. Identification and selection of manufacturing sites to be inspected:

i. Inspections will be conducted according to the approved target for each year.

ii. Scheduling of inspections will be initiated at least two (2) months before the tentative inspection dates.

iii. The Inspections Coordinator will, in liaison with the Assessors' Coordinator, identify sites for inspection from the AMRH database of applications received and the GMP database. Facilities will be selected based on a combination of, though not limited to, the following factors:

- The number of countries and or RECs in which applications have been lodged, priority being given to the facilities with the most significant number of applications common to the participating countries/ or RECs
- The priority needs for particular products
- First come, first served
- Level of compliance in the previous inspection

iv. The Inspections Coordinator will compile a list of eligible sites, guided by the annual target for the number of inspections. A contingency of one extra facility should be made in case the proposed inspection dates are unsuitable for any one facility.

b. Scheduling of selected companies:

i. A written Notice of Inspection, in accordance with the template appended as Annexure 2, will be issued to each manufacturing site:

- Requesting the current version of an electronic site master file
- Confirmation of dosage forms
- Proposed tentative inspection dates
    - Advising of a fee to be charged in accordance with Annexure 1

i. Upon receipt of the acceptance of the proposed

dates, the Inspections Coordinator will draw up a tentative itinerary and a budget for the trip. Inspection fees will be those approved by the AMRH Steering Committee (refer to Annexure 1).

ii. Allocation of dates and durations of inspection will be made based on the guidance in Annexure 1. In addition, one inspection report writing day will be allocated per site.

iii. The budget and itinerary will be submitted for approval to the Head of Programme, AUDA NEPAD

iv. On receipt of the approved budget and itinerary, the inspection coordinator will issue a proforma invoice to each site, with a deadline for the receipt of payment.

Inspection fees may be waived through the Head of Programme AUDA-NEPAD if alternative funding is available for the inspection.

c. Selection of inspectors

i. Each facility will be inspected by no less than two (2) inspectors from the AMRH pool of GMP inspectors, one of whom will be the Lead Inspector. Where there is financial support, and for training purposes, the inspection team will include additional inspectors and observers.

The inspection coordinator or programme secretariat from AUDA NEPAD may be co-opted to the inspections team for quality control purposes.

ii. The Inspections Coordinator will confirm the identity and availability of inspectors.

iii. The Lead Inspector will be chosen from the pool of competent and experienced inspectors who have, by mutual agreement, been deemed competent to lead inspections on behalf of AMRH or assessed to be at level 1 competency according to the AMRH or WHO inspector's competency framework.

iv. The Co-inspector will be chosen from the pool of competent and experienced inspectors who have, by mutual agreement, been deemed competent to conduct inspections on behalf of AMRH or assessed to be at level 1 or 2 competency according to the AMRH/WHO inspectors competency framework.

v. Observers may or may not have been assessed for competency in line with the AMRH/WHO inspectors' competency framework.

vi. In consultation with the GMP TC, the Inspections Coordinator will put in place a roster of GMP inspectors from a pool of AMRH competency-certified inspectors to select lead and co-inspectors.

vii. The team's composition can be augmented by an expert or mentor, who, for example, can be seconded by the WHO or the AMRH.

viii. The inspection coordinator will immediately share the approved plan with the nominated inspectors and request them to fill in the declaration of conflict of interest and confidentiality undertaking forms (Annexures 3 and 4, respectively).

d. Arranging travel logistics

i. The approved itinerary and budget will be forwarded to the AUDA NEPAD administration and logistics department to implement the logistics relating to travel arrangements and travel allowances. Logistics will be handled in accordance with the Agency's internal procedures for the same.

ii. Air tickets must be issued, and travel allowances must be paid out at least five days before travel.

iii. Preparation for the inspection will be handled in accordance with SOP # AMRH-GMP-002

- Procedure for Preparation for Inspections.

7. Records

The following records will be generated:

i. Notice of inspection

ii. Inspection itinerary

iii. Inspection schedule budget

8. References

i. Terms of Reference for AMRH GMP TC

9. Annexes

i. Table of Inspection Fees and Envisaged Inspection Days

ii. Notice of Inspection template

iii. Conflict of interest for AMRH inspectors

iv. Confidentiality undertaking

v. Flowchart

10. History and Authorisation

SOP	Date authorised	Reason for Change	Authorised by
00		New SOP	

ANNEXURE 1: TABLE OF INSPECTION ENVISAGED INSPECTION DAYS

	Facility Type	**Envisaged inspection days** *(Minimum as determined after evaluating the current SMF, the manufacturing lines, and the complexity of the product)* **any additional lines will entail additional inspection days and fees.* **Minimum three inspectors*
1	Non-Sterile plant (<3 dosage forms i.e. tablets & capsules and one other))	3
2	Sterile and special plant* (NB: plant with **svp** and powders treated as two different plants)	4
3	Biological plants, including vaccines (additional vaccine Drug substance on the same site, for same Drug product) (additional vaccine Drug substance, offsite)	5 2
4	Plants with three dosage forms applied for	4
5	Plants with more than three dosage forms applied for	5
6	Contract research organisations (CRO) and Quality Control Laboratories	3

* Special facilities include sterile products, special products, hormones, oncology, cephalosporin (injectable), penicillin (injectable), vaccines and biological products.

* The last inspection day will generate an interim report, discuss findings and conclude the inspection.

ANNEXURE 2: TEMPLATE - NOTICE OF INSPECTION

[Date]

[Company name & address]

Dear Sir/Madam,

RE: INSPECTION OF A MANUFACTURING PREMISES: [COMPANY NAME & ADDRESS]

Reference is made to the products from the above-mentioned premises that are under evaluation for registration under the AMRH GMP inspections initiative. Please be advised that an inspection team from the African Medicines Regulatory Harmonisation comprising of inspectors from **[indicating team composition in terms of countries]** would like to schedule the inspection of your premises as part of the assessment for the registration of [Product names and strengths]. **Please note that the inspection will focus on [indicate scope, e.g. tablets only]**, with particular emphasis on [Product names and strengths].

Kindly note that the inspection report will be shared by the participating countries and potentially with other AMRH Member States. In that regard, acceptance of this inspection will signify acceptance of this sharing arrangement. You may be requested to sign a release letter during the inspection.

An applicable inspection fee **will** be required for the inspection following the submission of an up-to-date site master file, which must be paid before the inspection.

We seek to advise that the inspection to verify compliance with current Good Manufacturing Practices (cGMP) has been scheduled from the **[indicate proposed tentative dates].**

Kindly confirm acceptance of the inspection and its terms and conditions and proposed dates at your earliest convenience, in writing, by the **[indicate deadline for receipt of confirmation].**

Yours faithfully

ANNEXURE 3: DECLARATION OF INTEREST FOR AMRH GMP INSPECTORS

To ensure the highest integrity and public confidence in its activities, AMRH requires that inspectors disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All inspectors must disclose any circumstances that could represent a **potential conflict of interest** (i.e., any interest that may affect, or may reasonably be perceived to affect, the inspector's objectivity and independence). You must disclose on this Declaration of Interests (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting you have been asked to participate in or contribute to and any interest that could be affected by the outcome of the meeting or work. You must also declare the relevant interests of your immediate family members (see definition below) and, if you are aware of it, the relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department). Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead AMRH to decide not to appoint you to the AMRH inspectorate in the future.

Please complete this form and submit it to the AMRH Secretariat, if possible four weeks but no later than two weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information before or during the meeting or work. All inspectors must complete this form before participation in AMRH activity can be confirmed. Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead AMRH to decide not to appoint you to the AMRH inspectorate in the future.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in AMRH activity. The Secretariat will review your answers to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g., nature and magnitude, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If a declared interest is determined to be potentially or patently significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision-making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity, and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage declared interests will be **published** in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside AMRH if the AMRH considers such disclosure to be in the best interest of the Organisation, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist, and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

Name:
Institution:
Email:

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organiser of the activity):

To participate in the AMRH inspection (Inspections Coordinator to insert inspection details with dates)

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, a research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organisation" includes a governmental, international or non-profit organisation. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past four years, have you received remuneration from a commercial entity or other organisation with an interest related to the subject of the meeting or work?

1a Employment Yes ☐ No ☐

1b Consulting, including service as a technical or other advisor Yes ☐ No ☐

RESEARCH SUPPORT

Within the past four years, have you or your research unit received support from a commercial entity or other organisation with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding Yes ☐ No ☐

2b Non-monetary support valued at more than US $1000 overall (include equipment, Yes ☐ No ☐

facilities, research assistants, paid travel to meetings, etc.)Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organisation with an interest related to the subject of the meeting or work?

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications) Yes ☐ No ☐

4b Proprietary know-how in a substance, technology or process Yes ☐ No ☐

PUBLIC STATEMENTS AND POSITIONS (during the past three years)

5a As part of a regulatory, legislative or judicial process, have you provided an inspector opinion or testimony related to the subject of the meeting or work, for a commercial entity or other organisation? Yes ☐ No ☐

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? Yes ☐ No ☐

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? Yes ☐ No ☐

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect the interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes ☐ No ☐

6c Excluding AMRH, has any person or entity paid or contributed towards your travel costs in connection with this AMRH meeting or work? Yes ☐ No ☐

6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly about this AMRH meeting or work? Yes ☐ No ☐

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes ☐ No ☐

7. TOBACCO OR TOBACCO PRODUCTS
(answer without regard to relevance to the subject of the meeting or work)

Within the past four years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? Yes ☐ No ☐

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is **"yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.**

Nos. 1 - 4: Type of interest, question number and category (e.g., Intellectual Property 4.a copyright) and basic descriptive details.	**Name of company, organisation, or institution**	**Belongs to you, a family member, an employer, a research unit or other?**	**Amount of income or value of interest (if not disclosed, is assumed to be significant)**	**Current interest (or year ceased)**
Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details				

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to disclose any relevant conflicts to other meeting participants and in the resulting report or work product. The disclosures will be evaluated by the AMRH secretariat, who will determine the impact of the declarations on the work to be performed and continued participation in the assignment.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of the AMRH and complete a new declaration of interest form that describes the changes. This includes any change before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date:_____ Signature:_____

ANNEX 4: CONFIDENTIALITY UNDERTAKING

CONFIDENTIALITY UNDERTAKING

Should be sent with the invitation and appointment letter

As a member of the African Medicines Regulatory Harmonisation (AMRH) inspection team, I will have access to confidential information related to *[Company]*_____, which AMRH considers to be proprietary to itself or to parties collaborating with it. As a member of the team, I undertake

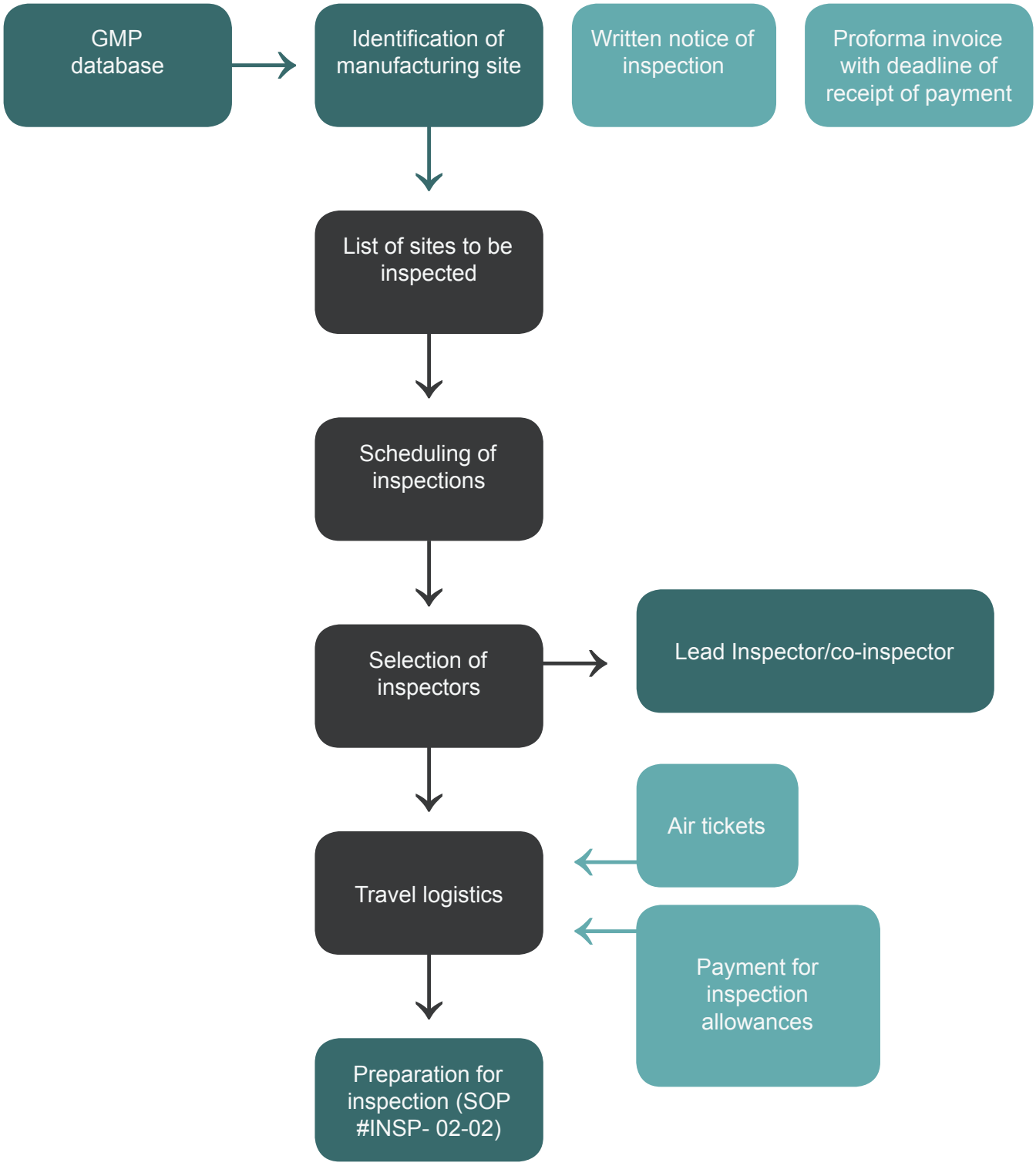
a. To take all possible steps to preserve strict confidentiality regarding any information I have access to through my work.

b. To never pass any information obtained as part of the inspection to anyone outside the inspection team, unless I have been directed to do so by a more senior team member, and reasons for doing so are clearly understood.

I understand that any breach of the above will result in disciplinary action.

Signed: _____ Date:_____

ANNEX 5: SCHEDULING OF INSPECTIONS FLOWCHART



AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for Preparation for GMP Inspections

1. Policy

All AMRH GMP inspectors will prepare adequately for each inspection and ensure they are equipped with all the pertinent documents relating to the site(s) inspection to ensure a consistent approach to conducting continental AMRH inspections.

Inspection preparedness must involve communicating the tentative inspection plan/agenda with the company to be inspected.

2. Scope

This procedure applies to all inspection schedules under the AMRH GMP inspections collaboration. It will be used by all AMRH GMP inspectors

3. Purpose

This procedure is intended to guide the adequate preparation for inspections.

4. Definitions

- AMRH – African Medicines Regulatory Harmonisation. This term will be replaced with the African Medicines Agency once it becomes operational.
- Per diem – travel and subsistence allowance given to cover the cost of accommodation, meals and any other travel incidental expenses.

5. Responsibility

i. AMRH GMP Inspections Coordinator

- Identify the manufacturing sites requiring inspection in accordance with SOP for Scheduling of Inspections.
- Select the Lead Inspector and inspection team in consultation with the heads of inspectorates within the region.
- Prepare logistics requirements for inspection.

ii. Lead Inspector

- Prepare the inspection agenda and send it in advance to the manufacturer.
- Communicate with the companies and circulate information among the co-inspectors.
- Prepare the list of required documents to be ready during inspection.

iii. Lead Inspector and Co-inspector(s) – review documents relevant to the inspection and circulate for review all information that may be pertinent to the inspection.

6. Procedure

a. Confirmation of manufacturing sites to be inspected:

i. The Lead Inspector will obtain a copy of the approved itinerary from the Inspections Coordinator.

ii. The Lead Inspector will confirm the objective and scope of the inspection by verifying the identity of products manufactured/tested at each site. This may entail communication with the Inspections Coordinator, who will be in liaison with the Dossier Assessors Coordinator.

b. Communication

i. The Lead Inspector will request for the following from the Inspections coordinator:

- An electronic (soft) copy of the current version of the Site Master File according to the WHO-prescribed format,
- Confirmation of the list of the products manufactured by the facility for which applications have been submitted for registration under the AMRH collaborative initiative. Any disparity between the manufacturer and the list of products obtained from the AMRH database will be communicated immediately to the Assessors Coordinator.
- Invitation letters for visa applications (where necessary), and assistance with accommodation and local travel bookings,
- The site contact persons' details for further communication
- Assessment report(s) of the products under consideration by the assessors.

ii. The Lead Inspector will verify any previous inspections and extract the respective reports from the database or the Inspections Coordinator.

iii. The Lead Inspector will circulate the information to the co-inspectors.

c. Preparation for inspections:

i. Once appointed to an inspection schedule, inspectors will complete the logistics checklist given in Annexure 1. The checklist must be completed at least five (5) days before departure and submitted to the Inspections Coordinator. The Inspections Coordinator may make a call to go through the checklist accordingly.

ii. The Inspections Coordinator will immediately verify that travel and accommodation logistics, including *per diem* transfer, are in order and save a copy of the checklist. Any issues of concern should be reported to the Head of Programme responsible for logistics at AUDA NEPAD.

iii. Before conducting an inspection, the inspectors will familiarise themselves with each company to be inspected. This may include studying and making notes for following up based on the following:

- assessment of the Site Master File;
- review of the list of products manufactured by the company and those submitted for registration under AMRH to confirm the dosage forms that will be part of the scope of the inspection;
- review of the follow-up actions (if any) arising from previous inspections;
- review of the assessment reports of the products from the site. Quality information summaries can also be requested from the assessors;
- familiarisation with the relevant aspects of the manufacturing authorisation application of one or more selected products to be examined during the inspection;
- review of product recalls initiated in any of the countries in the African region and beyond;
- examination of relevant product defects notified since the previous inspection, if any;
- review of the analysis of any samples analysed by any of the active AMRH country Quality Control Laboratories;
- review of any special standards or guidelines associated with the scope of the inspection;
- review of variations to marketing authorisations applied for, granted and refused;
- review of pertinent information available on regulatory databases (Eudra GMP, FDA warning letters, public shared network, Mednet, WHO, etc.);
- a review (or preparation) of aide-mémoires for the specific inspection to avoid missing important aspects of GMP/GCP/GLP.

d. Preparation of inspection plan:

Inspectors will prepare an inspection plan/agenda (Annexure 2), which should reflect the following:

- the objectives and the scope of the inspection;
- identification of the inspection team members and their respective roles;
- the date and place where the inspection is to be conducted;
- identification of the manufacturing blocks and organisational units to be inspected;
- the expected time and duration for each major inspection activity (premises, processes, etc.);
- the schedule for the final meeting;
- the approximate timelines applicable to the inspection process, including transmission of the inspection report and submission of the response.

7. Records

i. Inspection plan/agenda

8. References

i. WHO Technical Report Series (TRS), No 986 of 2014

ii. WHO Technical Report Series (TRS), No 999 Annexure 2

iii. SADC MRH Zazibona GMP inspections

9. Annexures

iv. Logistics checklist

v. Tentative inspection plan template

vi. Flowchart

10. History and Authorisation

SOP Version	Date authorised	Reason for Change	Authorised by
00		New SOP	

ANNEXURE 1: PREPARATION (LOGISTICS) CHECKLIST

Manufacturer/CRO	
Address:	
Dates of inspection:	
Inspectors:	

No.	Actions	Yes	No	Date
Part 1: communication with the manufacturer				
1.	Manufacturer/CRO liaison person identified and contacted			
1.1	Invitation letters for visa applications requested and received			
1.2	Accommodation quotations and booking assistance requested			
1.3	Local travel arrangements requested, including airport pick-up and drop-off			
1.4	Current version of the SMF requested			
1.5	Last APQR report for the product/s of interest			
Part 2: financial issues				
2.1	Inspectors' bank details and passport copies submitted to administrative staff handling logistics			
2.2	Booking of flight and domestic transportation			
2.3	Booking of Accommodation and hotel			
Part 3: Manufacturer/CRO historical data reviewed				
3	Manufacturer/CRO historical data reviewed:			
3.1	• Previous inspections report(s)			
3.2	• Correspondence			
3.3	• Corrective actions			
3.4	• Adverse drug reaction reports			
3.5	• Complaints and recalls			
Part 4: list of required documents to be prepared before the inspection				
4.1	SMF reviewed and follow-up questions drawn up			
4.2	Product assessment reports reviewed			
4.3	Checklist or aide-mémoire prepared			

4.4	Draft inspection programme/agenda prepared and circulated amongst inspectors			
4.5	Draft inspection programme/agenda sent to the manufacturer			
Part 5: logistics confirmed seven days before travel				
5.1	Travel arrangements confirmed			
5.2	E-tickets received			
5.3	*Per diem* received			
5.4	Accommodation bookings confirmed			
5.5	Logistics checklist submitted to the AMRH Inspections Coordinator			

ANNEXURE 2: TENTATIVE INSPECTION PLAN/AGENDA

Manufacturer/CRO	
Address:	
Dates of inspection:	
Inspectors:	

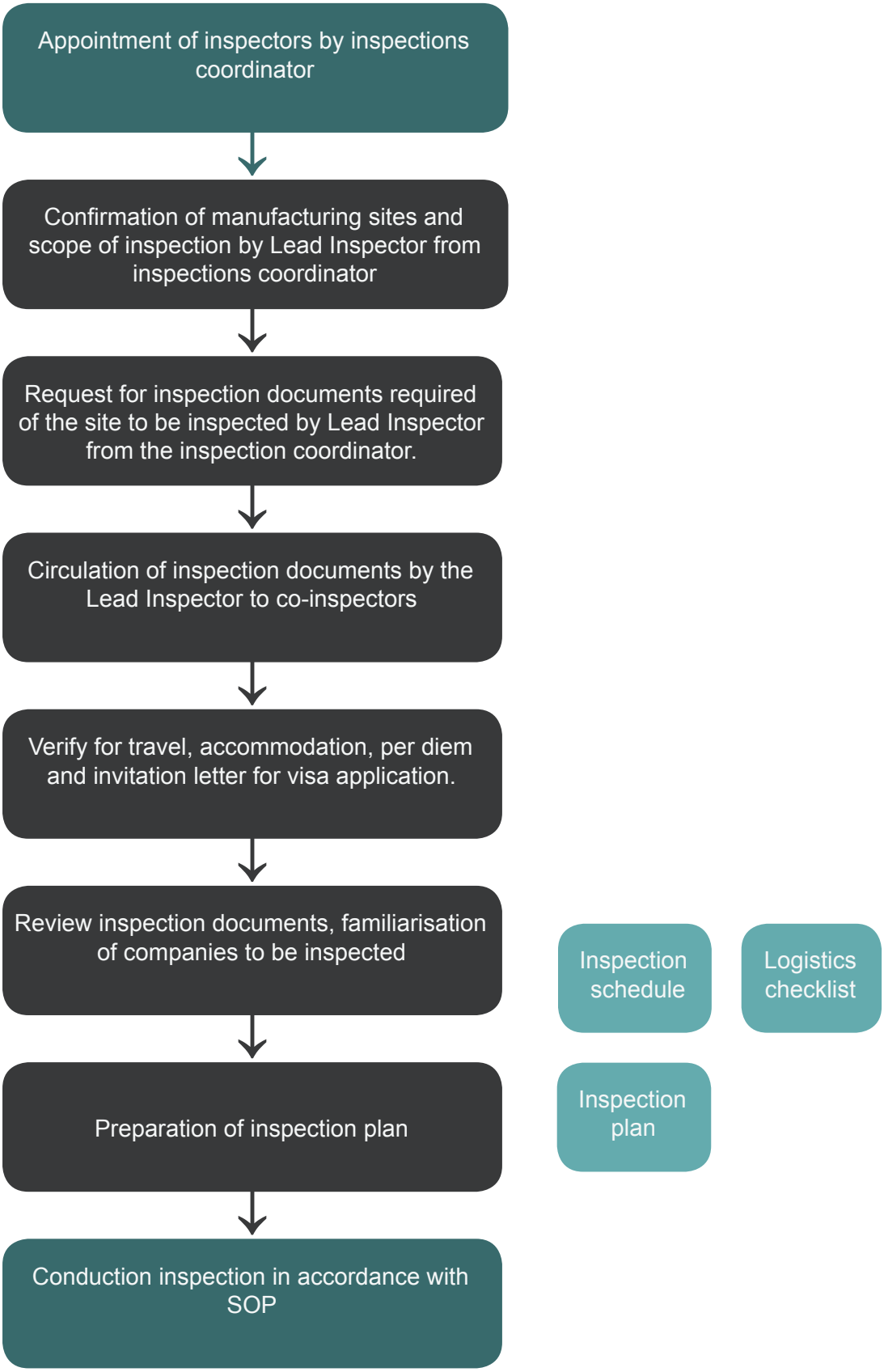
Day 1 - Morning	
Opening Meeting – 09:00	Introductions
	Objectives and scope of the inspection, including an overview of the AMRH inspection process and timelines for interim report, final report and CAPA submission
	Confirmation of the proposed inspection agenda
	Brief company presentation of the factory
	Recent changes
Document Review	Quality system (Self-inspections, outsourcing, batch release, management quality reviews, OOS, Deviations, Changes) – SOPs and log books/records
	Quality Manual and/or quality policy
	Validation Master Plan and validation files for product/s of interest (process validation, cleaning validation, HVAC validation, gases, purified water system, analytical methods, computer systems as applicable).
	Change control and deviation management: SOPs + summary list of changes and deviations
	Annual product quality review reports for products of interest
	Risk management SOP and log book
	Complaints: SOP + summary list of complaints
	Recalls: SOP + summary list of recalls
	Site plan, production block layout, indicating the HVAC system and AHUs, material and personnel flow
	HVAC system schematic drawing and summary of specifications for HVAC
	Purified water system plan and summary of specifications for PW
	Compressed air system schematic drawing and summary of specifications for compressed air
Day 1 – up to 17:00	
Site Inspection	Receiving area and stores
	Starting materials, packaging materials and components
	Finished products
	Sampling, dispensing and issuing
Day 2 - Morning	

Continuation Of Site Inspection	Production of tablets - following material flow
Day 2 - Afternoon	
Inspection Of Production Activities	Production of tablets - continuation Utilities • HVAC system • PW system • Compressed air system
Day 3 - Morning	
Laboratory	Wet chemistry laboratory
Inspection	Instrumental laboratory
	Laboratory materials management
	Microbiological laboratory
	Retention samples storage
Day 3 - Afternoon	
Documents Review	Review of remaining documents Follow up on issues
Closing Meeting	Approximately 4.30 pm

Notes:

1. Note that additional documents may be requested on the day of the inspection.
2. Tea and lunch breaks will be taken at suitable times, on-site or in close proximity, to avoid time losses.
3. The inspection will start at approximately 08:30 and finish at approximately 17:00 each day and/or in line with the facility's working times.
4. At the end of each day, a brief meeting will be held to review the findings and discuss the plan for the next day. A feedback meeting will be held each morning before the start of the next day.
5. The company should provide appropriate personal protective equipment (PPE) for the inspectors.
6. All necessary national or global health precautions should be followed as applicable

ANNEXURE 3: PREPARATION FOR INSPECTION FLOWCHART



AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for Conducting GMP Inspections

1. Policy

To ensure uniformity and consistency of AMRH GMP inspections, there will be strict adherence to this procedure and stipulated timelines.

2. Scope

This procedure applies to GMP inspections carried out by AMRH GMP inspectors for pharmaceutical, vaccines, biological and medical products.

3. Purpose

This SOP aims to outline a standardised procedure to be followed by all inspectors within the AMRH collaborative initiative when conducting GMP inspections.

4. Definitions

- AMRH Inspections coordinator- a member of the secretariat assigned to carry out the roles of coordinating the continental inspections and inspection activities.
- AMRH – African Medicines Regulatory Harmonisation. This term will be replaced with the African Medicines Agency once it becomes operational.

5. Responsibility

AMRH GMP Inspection Coordinators:

- select the inspection team
- plan for the AMRH inspections
- arrange logistics for conducting the inspection
- communicate with the manufacturer to have the required documents ready during the inspection
- organise the communication between the inspection team and the manufacturer before, during and after the inspection

Team leader inspector:

- prepare a list of the required translated documents
- assign tasks during inspection between the inspection team
- collect observations from inspectors
- write the final inspection report
- lead opening and close meeting
- send the final report to the manufacturer and receive feedback on corrective action
- attendance records and cover letters for inspection reports will be done by the Lead Inspector on AMRH letterhead

Inspectors:

- conduct the inspections
- collect evidence and review documents
- performs tasks assigned to them by the leader
- write initial observations according to the reference guide
- signed the final report
- review the corrective action submitted

6. Procedure

a. Opening meeting

i. After arrival at the site, inspectors will start the inspection with an Opening Meeting, which should last no more than 30 minutes.

ii. The inspection team leader starts the opening meeting by introducing the inspection team accompanying him and the purpose of the inspection. The leader then discusses the inspection agenda, sent in advance, with key persons in the manufacturing department and agrees on its final form.

The Lead Inspector should:

- outline AMRH activities, the purpose and scope of the inspection, including confirmation that the inspection is conducted in accordance with current WHO Guidelines as set out in the appropriate Technical Report Series;
- circulate an attendance record, the template for which will bear the AMRH letterhead.
- request the company to keep the necessary documents ready during the inspection, as well

as declare expectations in terms of timelines for document retrieval

- request or allow the company to make a brief presentation, which should take no more than 15-20 minutes.

iii. During the opening meeting, the company should:

- describe the Quality Management System;
- Explain significant changes in facilities, equipment, products and personnel since the last inspection conducted by any of the AMRH countries or within five years preceding the inspection.
- If the AMRH is inspecting the facility for the first time, a detailed facility description should be given.
- explain how deficiencies have been resolved if this information has not already been forwarded to the agencies;
- designate the people to accompany the inspectors during the inspection;
- discuss appropriate times for breaks to minimise disruption to the inspection process
- allocate a room for the inspectors when requested.

b. Inspection of plant facilities:

***The inspection should be carried out in accordance with the HRMA GMP initiative guideline, GL-HRMA-GMP-001.**

i. In order to assess compliance with the terms and conditions of the manufacturing authorisation, a general inspection normally includes, but is not limited to, an examination of the following key GMP systems :

1. Pharmaceutical quality system
    a. Quality risk management
    b. Product quality review
2. Good manufacturing practice for pharmaceutical products
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
    a. General
    b. The originator
    c. The acceptor of the contract
    d. The contract
8. Self-control, quality audits, supplier audits and approval
    a. Elements for self-inspection, self-inspection team, frequency of self-inspection, self-inspection report, follow-up measures,
    b. Quality audit,
    c. Supplier audits and approval
9. The staff
    a. General
    b. Key personnel
10. Training
11. Personal hygiene
12. Premises
    a. General
    b. Ancillary areas
    c. Storage areas
    d. Weighing areas
    e. Production areas
    f. Quality control areas
13. Equipment
14. Materials
    a. General
    b. Starting materials
    c. Packaging materials
    d. Intermediate and bulk products
    e. Finished products
    f. Rejected, recovered, reprocessed and reworked materials
    g. Recalled products
    h. Returned goods
    i. Reagents and culture media
    j. Reference standards
    k. Waste
    l. Miscellaneous

15. Documentation

    a. General
    b. Documents required

16. Good manufacturing practice

    a. General
    b. Prevention of cross-contamination and bacterial contamination during production
    c. Processing operations
    d. Packaging operations

17. Good quality control practices

    a. Control of raw materials and intermediate, bulk and finished products
    b. Testing requirements
    c. Examination of batch records
    d. Stability studies
    e. References

ii. In order to assess compliance with the marketing authorisation specifications, a product-based inspection will typically be carried out, involving the examination of specific documentation relating to one or more finished batches of a specified product, including;

    i. Standard Operating Procedures (SOPs) ;

    ii. Process validation

    iii. Product quality review ;

    iv. Manufacturing formulas, records and instructions;

    v. Specifications, sampling and methods of analysis of components, raw materials, intermediate products and finished products.

iii. The inspection must be carried out in accordance with the agreed inspection plan, which may be adapted if necessary.

The inspection

- should check the suitability of the premises using floor plans to explain the flow of people, materials and pressure differentials.

- can be carried out by means of a detailed visit to the plant to determine whether the plant and equipment are well laid out and designed, and whether the way in which they are used corresponds to the planned operations. In some cases, an immediate inspection after arrival on site may be useful.

iv. A risk-based approach to conducting the inspection would be to look for signals indicating a problem with a product, process or system and then focus the inspection on these areas and, as such, keep a flexible inspection plan. Likewise, identifying a high risk during the inspection could occasion a change in the inspection plan, causing it to go deeper into the specified area.

v. Where applicable, it may be appropriate to concentrate efforts in one department of the company if there are particular problems or requirements, e.g. a department only producing sterile dosage forms or non-sterile dosage forms. Relevant service areas should include, e.g. water, steam and ventilation/dust extraction systems and engineering support.

vi. During the inspection, the inspectors should always discuss observations with the key personnel, supervisors and operators as they arise to establish facts, indicate areas of concern, and assess the knowledge and competence of these personnel.

vii. Where necessary, exhibits (uncontrolled reference/ information copies) of documents or records or risk-based product samples may need to be taken.

viii. There must be a review of the documentation system. The whole system, including but not limited to specifications, manufacturing formulae, processing and packaging instructions, procedures and records covering the different production, QC and distribution operations, should be checked by examining particular examples both during use and after compilation into complete batch records. The documentation review will mainly focus on the products under consideration in terms of the inspection scope.

ix. No deficiencies should be included in the report if these were not mentioned/discussed with the company. In that regard, inspectors should provide feedback to the company (deficiencies) made during the inspection. This can be done at the end of each day, in the morning of the next day or at the end of the inspection.

x. Where products are approved within the region, the Lead Inspector should notify the inspection

coordinator immediately of any immediate risks to public health and confirm this concern during the closing meeting. The Inspections Coordinator will evaluate with the GMP TC within 24 hours and, in turn, bring the risks to the attention of the Heads of Agencies within 24-48 hours for appropriate national decisions.

c. Closing Meeting

i. When the inspection has been completed, the Lead Inspector should arrange a closed meeting between inspectors to discuss the deficiencies in preparation for the closing meeting. During this "closed meeting of inspectors", the team should agree on the final feedback to be provided to the company.

ii. The Lead Inspector should summarise the findings during the final meeting with company representatives, usually the technical management, including key personnel and preferably some or all of the senior management if these differ from the key personnel.

iii. The final meeting is a significant part of the inspection. The deficiencies observed during the inspection should be discussed. Their importance should also be discussed so that appropriate deadlines for remedial actions may be fixed,

iv. The company should preferably agree to objective evidence supporting the observations. This should also allow the company to initiate the necessary corrective actions as soon as possible.

v. The relevant Critical and Major observations must be captured in the Interim Inspection Report, a copy of which must be given to the company within 24 hours after the closing meeting. The Interim Report should be generated in accordance with the SOP for Inspection Reporting. The Interim Inspection Report should also be emailed to the Inspections Coordinator and Focal Persons at the GMP TC.

vi. Outline the next steps, including the expectations and timelines for submitting the Corrective and Preventive Action Plans.

vii. The final inspection report should be prepared in accordance with SOP for Inspection Reporting

7. Records

i. meeting attendance record – AMRH letterhead

ii. record of copies of any documents requested and collected during the inspection

iii. Interim Inspection Report

8. References

i. WHO Technical Report Series (TRS), No. 986 of 2014.

ii. SADC MRH, Zazibona SOP on GMP inspections

9. Annexures

i. Interim Inspection Report template

ii. Flowchart

10. History and Authorisation

SOP Version	Date authorised	Reason for Change	Authorised by
SOP/AMRH/GMP/001	TBA	New SOP	

ANNEXURE 1: TEMPLATE - INTERIM INSPECTION REPORT

(WHO TRS 996 Annexure 4- Model GMP inspection report)

AMRH GMP INSPECTION PROGRAMME

INTERIM GMP INSPECTION REPORT OF PHARMACEUTICAL MANUFACTURER:

[COMPANY NAME, ABRIDGED ADDRESS]

Part 1: General information

Name of the audited company	
Physical address	
Summary of the main activities performed	
Scope of inspection	
Purpose of inspection	
Contact person(s)	
Quality Assurance	
Inspectors	
Personnel who attended the opening meeting	
Date of inspection	

[FOOTER]: Interim GMP Inspection Report, *[company name, manufacturing site address & inspection dates]* Page x of y

List of abbreviations

1. GMP: Good manufacturing practices
2. SOP: Standard operating procedures
3. WHO: World Health Organisation
4. HVAC: Heating, ventilation, and air conditioning
5. TRS: Technical Report Series
6. WFI: water for injection

Definitions

For the observations, the reference numbers below in the right-hand column refer to the relevant clause(s) of the WHO Good Manufacturing Practices detailed in the WHO Technical Report Series 986, 2014.

Observations are classified into the categories “Critical”, “Major”, and “Other (Minor)” and also in accordance with the functions related to manufacturing as provided for in the WHO TRS986.

1. **Critical Observation:** An observation that has produced or may result in a significant risk of manufacturing products that are harmful to the user.
2. **Major Observation:** A non-critical observation that:

- has produced or may produce a product that does not comply with its specifications; and/or
- indicates a major deviation from the GMP guidelines and/or
- indicates a failure to carry out satisfactory procedures for the release of batches and/or
- indicates a failure of the person responsible for QA/QC to fulfil their duties and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such

3. **Other Observation:** An observation that cannot be classified as either critical or major but indicates a departure from good manufacturing practice. A deficiency may be classified as “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical

Part 2: Summary

The manufacturing site of [Company Name] is located at [Company address] and was inspected by the AMRH inspection team from the [inspection dates].

[other facts, for example: company overview; scope of inspection including the products under consideration; and a brief description of the inspection process, i.e. major events such as opening meeting, etc.]
The inspection was conducted with reference and in accordance with the Quality Assurance of Pharmaceuticals, the WHO Good Manufacturing Practices detailed in the **WHO Technical Report Series 986 of 2014-Annexure 2 and other WHO GMP publications (or their current publications).**

Areas inspected

Detailed summaries of the GMP systems and utilities inspected should be given, quoting applicable references of documents reviewed during the inspection. GMP systems not assessed during the inspection must be clearly highlighted.

List of documentation reviewed during the inspection

- [list of SOPs and other documents] *(Including name, number and version of SOP or document)*

Production activities

- [Description of the manufacturing activities done at the facility, including the actual production activities observed during the inspection]

Quality Control

- [Description of the Quality Control activities, including microbiology, technology available, outsourcing and application of laboratory quality systems and good laboratory practice).

Part 3: Observations

NR	Observations	WHO GMP Reference
	Critical	
	Major	
	Others	

Part 4: Conclusion

Based on the areas inspected, personnel interviewed and documents reviewed and considering findings during the inspection, which include the observations listed in the inspection report, a decision on the compliance of **[company name and address]** with WHO guidelines for the manufacture of [scope, e.g. oral solid dosage form] **will be made after the manufacturer's response to the observations has been assessed.**

The manufacturer must respond to the **final report observations** where, for each one, a description of the corrective action implemented or planned to be implemented and the target date of completion are included.

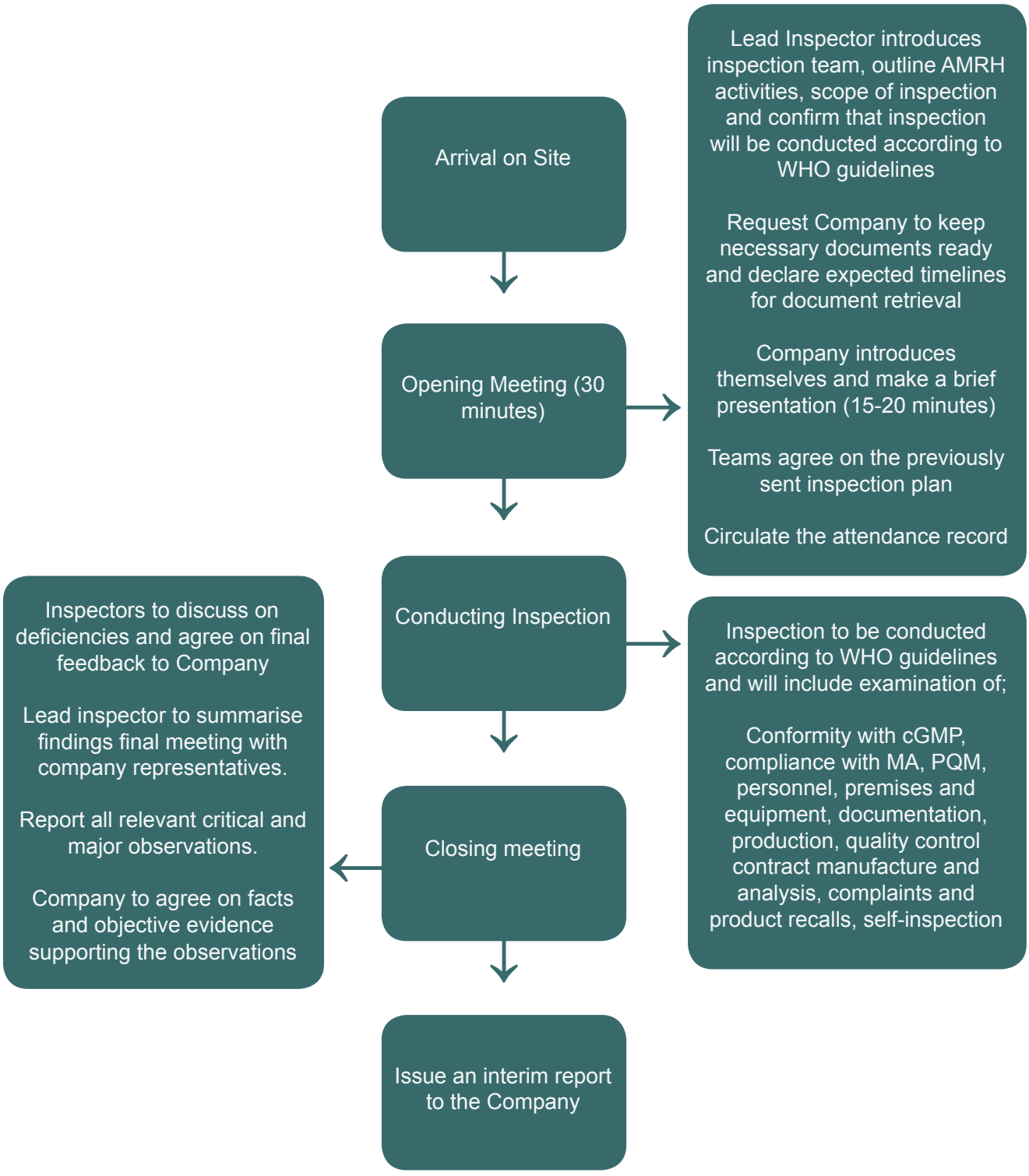
_____ Date _____

(Lead Inspector)

List of other accompanying inspectors/personnel

Sr. No.	Name	Institution/Country	Role in the inspection

ANNEXURE 2: CONDUCTING INSPECTION



AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for GMP Inspection Reporting

1. Policy

- Accurate records of all inspections must be maintained, including all communications with the company for each inspection.
- Uniformity and consistency in the approach are required to build confidence in the initiative, and to ensure that any variance in inspection outcomes is based purely on the company's quality system and not operational issues within the regulatory harmonisation initiative.
- The inspection report must provide a factual and objective record of the inspection that includes what was done, the inspection findings for each activity inspected, and a conclusion applicable to the time the report is written.
- Inspection reports should be written in the third person passive style and in the past tense.

2. Scope

This procedure applies to writing all the interim and final GMP inspection reports, compliance/CAPA report review and inspection closure letters by GMP inspectors under the AMRH GMP inspections collaboration.

3. Purpose

- This SOP aims to outline the standardised procedure for writing all AMRH GMP inspection reports and their follow-up.
- Documenting all observations monitored in a simple and understandable manner, supported by evidence based on WHO reference requirements.

4. Definitions

i. AMRH Inspections coordinator- a member of the secretariat assigned to carry out the roles of coordinating the continental inspections and inspection activities.

ii. AMRH – African Medicines Regulatory Harmonisation. This term will be replaced with the African Medicines Agency once it becomes operational.

iii. AMRH GMP Technical Committee – a team of GMP experts selected from all the Regional Economic Communities (REC) of the African Union. They provide technical evaluation of the work and documents used by the AMRH GMP inspectorate.

5. Responsibility

i. All inspectors – following the procedure to document every GMP inspection

ii. AMRH Inspections Coordinator – ensuring the procedure is followed every time, and that all reports and CAPAs are appropriately maintained and archived.

iii. Lead Inspector – accurately documenting the inspection they lead and accurately recording every observation made during the inspection.

iv. AMRH GMP Technical Committee – actively participating and contributing to reviewing the final inspection report and CAPA, leading to an appropriate recommendation.

6. Procedure

a. Compiling the GMP Inspection Interim Report:

i. As the Lead Inspector, take the lead in documenting the inspection. At the end of the first day of inspection, lead the team to begin writing the interim report by filling in all administrative sections, Part 1 and Part 2, as per the template in Annexure 1 and WHO TRS996 Annexure 4's WHO Model Inspection report. Make use of the current site master file, introductory site presentations and attendance registers for the opening meeting and document request forms.

ii. At the end of each day, the team leader will be responsible for holding a review meeting with all inspectors present and writing all observations from that day into the appropriate classification section, i.e. Critical/Major/Other.

iii. At the end of the last inspection day, the observations list should be updated to include all observations recorded during all inspection days.

iv. Ensure the accuracy of the Interim Report through appropriate proofreading by the inspector(s) who did not write the report and make amendments if need be.

v. The Lead Inspector will present the Interim Report to the manufacturer's audit team in the closing meeting and discuss all the observations, at least all critical and significant observations and allow

the company to seek clarification, if needed, in the presence of all inspection team members

vi. After agreeing with the company representatives on the observations, the team leader will email the contact person a copy of the discussed Interim Report and copy the AMRH GMP Inspections Coordinator and the AMRH GMP TC.

Inspectors should avoid connecting to manufacturers' IT networks and instead transmit reports from a secure network if possible.

b. Compiling the GMP Final Inspection Report

i. Each inspection report will be issued a file name according to the following format: Company name, Location, _Unit/Block, _FPP, _Month, _Year

ii. On the allotted report writing days, finalise all the reports in that schedule by replacing the word "interim" with "final" on the interim report and adding more detail regarding the inspection process and the general findings (both positive and negative observations).

iii. Reference all the observations in accordance with the WHO publications on GMP. Other reputable non-WHO GMP publications, e.g., ISPE, PIC/S, and PDA, may be added if they will assist in making the observations clearer to the manufacturer.

iv. Proofread the entire report, ensuring there are no confusing statements, especially in the conclusion section of the report.

v. Email the co-inspector(s) a copy of the finalised report for proofreading and copy the Inspections coordinator.

vi. Circulate the final report for input and comments from the AMRH GMP TC within **ten working days** of the first working day after all inspectors have returned to their base stations.

vii. Convene a virtual meeting of the NRA AMRH GMP Focal Persons and the co-inspectors to discuss the final inspection report. The virtual meeting should be within **five working days** of circulation of the final report.

viii. With the consensus of the co-inspectors and focal persons, the final report must be signed on the last page. Endorse every page by writing your initials at the bottom of the pages. The co-inspector must also do the same.

ix. The Lead Inspector is to prepare a cover letter in accordance with **Annexure IV.** The cover letter must request the company to acknowledge receipt of the final inspection report and stipulate that a CAPA is required in the attached template and within **60** calendar **days** of receipt of the final inspection report, as well as instruct that the CAPA be submitted in both Word and PDF formats, together with two CD/pen drive copies of the comprehensive CAPA including all attachments.

x. Scan the signed cover letter and final report and send the scanned copy to the manufacturer's contact person(s) and copy the Inspections Coordinator and the Focal Persons within **30 days** from the last inspection on the inspection schedule.

7. Records

i. Interim Inspection Report

ii. Final Inspection Report

iii. Compliance Review Report

8. References

i. WHO Technical Report Series (TRS), No 996, Annexure 4

9. Annexures

i. Interim Inspection Report Template

ii. Final Inspection Report Template

iii. Corrective Action and Preventative Action format

iv. Inspection closure letter

v. Flowchart

10. History and Authorisation

SOP Version	Date authorised	Reason for Change	Authorised by
00		New SOP	

ANNEXURE I: INTERIM INSPECTION REPORT TEMPLATE

(WHO TRS 996 Annexure 4- Model GMP inspection report)

AMRH GMP INSPECTION PROGRAMME

INTERIM GMP INSPECTION REPORT OF PHARMACEUTICAL MANUFACTURER:

[COMPANY NAME, ABRIDGED ADDRESS]

Part 1: General information

Name of the audited company	
Physical address	
Summary of the main activities performed	
Scope of inspection	
Purpose of inspection	
Contact person(s)	
Quality Assurance	
Inspectors	
Personnel who attended the opening meeting	
Date of inspection	

[FOOTER]: Interim GMP Inspection Report, *[company name, manufacturing site address & inspection dates]* Page x of y

Part 2: Summary

The manufacturing site of [Company Name] is located at [Company address] and was inspected by the AMRH inspection team from the [inspection dates].

[other facts, for example: company overview, scope of inspection including the products under consideration and brief description of the inspection process, i.e. major events such as opening meeting etc.]
The inspection was conducted with reference and in accordance with the Quality Assurance of Pharmaceuticals and the WHO Good Manufacturing Practices detailed in the **WHO Technical Report Series 986 of 2014-Annexure 2 and other WHO GMP publications.**

Areas inspected (This section may be skipped in the interim report, but detailed in the final report)

Summaries of the GMP systems and utilities inspected should be given, quoting applicable references of documents reviewed during the inspection. GMP systems not assessed during the inspection must be clearly highlighted.

List of documentation reviewed during the inspection

- [list of SOPs and other documents] (Including name, number and version of SOP or document)

Production activities

- [Description of the manufacturing activities done at the facility, including the actual production activities observed during the inspection]

Quality Control

- [Description of the Quality Control activities, including microbiology, technology available, outsourcing and application of laboratory quality systems and good laboratory practice).

Part 3: Observations

List of abbreviations

7. GMP: Good Manufacturing Practices
8. SOP: Standard Operating Procedures
9. WHO: World Health Organisation
10. HVAC: Heating, Ventilation, and Air Conditioning
11. TRS: Technical Report Series
12. WFI: Water for Injection

Definitions

For the observations, the reference numbers in the right-hand column below refer to the relevant clause(s) of the WHO Good Manufacturing Practices detailed in the WHO Technical Report Series 986, 2014.

Observations are classified into the categories “Critical”, “Major”, and “Other (Minor)” and also in accordance with the functions related to manufacturing as provided for in the WHO TRS986.

4. **Critical Observation:** An observation that has produced or may result in a significant risk of creating products that are harmful to the user.

5. **Major Observation:** A non-critical observation that:

- has produced or may produce a product that does not comply with its specifications; and/or
- indicates a significant deviation from the GMP guidelines; and/or
- indicates a failure to carry out satisfactory procedures for the release of batches; and/or
- indicates a failure of the person responsible for QA/QC to fulfil their duties; and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such

6. **Other Observation:** An observation that cannot be classified as critical or major but indicates a departure from good manufacturing practice. A deficiency may be classified as “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical

NR	Observations	WHO GMP Reference
	Critical	
	None	
	Major	
	Others	

Part 4: Conclusion

Based on the areas inspected, personnel interviewed and documents reviewed and considering findings during the inspection, which include the observations listed in the inspection report, a decision on the compliance of **[company name and address]** with WHO guidelines for the manufacture of [scope, e.g. oral solid dosage form] **will be made after the manufacturer's response to the observations has been assessed.**

The manufacturer must respond to the **final report observations** where, for each one, a description of the corrective action implemented or planned to be implemented and the target date of completion are included.

_____ Date _____

(Lead Inspector)

List of other accompanying inspectors/personnel

Sr. No.	Name	Institution	Role in the inspection

ANNEXURE II: FINAL GMP INSPECTION REPORT TEMPLATE

(WHO TRS 996 Annexure 4- Model GMP inspection report)

ANNEXURE 1: TEMPLATE - FINAL INSPECTION REPORT

AMRH GMP INSPECTION PROGRAMME

INTERIM GMP INSPECTION REPORT OF PHARMACEUTICAL MANUFACTURER:

[COMPANY NAME, ABRIDGED ADDRESS]

Part 1: General information

Name of the audited company	
Physical address	
Summary of the main activities performed	
Scope of inspection	
Purpose of inspection	
Contact person(s)	
Quality Assurance	
Inspectors	
Personnel who attended the opening meeting	
Date of inspection	

List of abbreviations

1. GMP: Good Manufacturing Practices
2. SOP: Standard Operating Procedures
3. WHO: World Health Organisation
4. HVAC: Heating, Ventilation, and Air Conditioning
5. TRS: Technical Report Series
6. WFI: Water For Injection

Definitions

For the observations, the reference numbers in the right-hand column below refer to the relevant clause(s) of the WHO Good Manufacturing Practices detailed in the WHO Technical Report Series 986, 2014.
Observations are classified into the categories “Critical”, “Major”, and “Other (Minor)” and also in accordance with the functions related to manufacturing as provided for in the WHO TRS986.

1. **Critical Observation:** An observation that has produced or may result in a significant risk of creating products that are harmful to the user.
2. **Major Observation:** A non-critical observation that:

- has produced or may produce a product that does not comply with its specifications; and/or
- indicates a significant deviation from the GMP guidelines; and/or
- indicates a failure to carry out satisfactory procedures for the release of batches; and/or
- indicates a failure of the person responsible for QA/QC to fulfil their duties; and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such

3. **Other Observation:** An observation that cannot be classified as critical or major but indicates a departure from good manufacturing practice. A deficiency may be classified as “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical

Part 2: Summary

The manufacturing site of [Company Name] is located at [Company address] and was inspected by the AMRH inspection team from the [inspection dates].

[other facts, for example: company overview; scope of inspection including the products under consideration; and brief description of the inspection process, i.e. major events such as opening meeting, etc.]

The inspection was conducted with reference and in accordance with the Quality Assurance of Pharmaceuticals and the WHO Good Manufacturing Practices detailed in the **WHO Technical Report Series 986 of 2014 Annexure 2 and other WHO GMP publications (or the current publications thereof).**

Areas inspected

Detailed summaries of the GMP systems and utilities inspected should be given, quoting applicable references of documents reviewed during the inspection. GMP systems not assessed during the inspection must be clearly highlighted.

List of documentation reviewed during the inspection

- [list of SOPs and other documents] (Including name, number and version of SOP or document)

Production activities

- [Description of the manufacturing activities done at the facility, including the actual production activities observed during the inspection]

Quality Control

- [Description of the Quality Control activities, including microbiology, technology available, outsourcing and application of laboratory quality systems and good laboratory practice).

Part 3: Observations

NR	Observations	WHO GMP Reference
	Critical	
	Major	
	Others	

Part 4: Conclusion

Based on the areas inspected, personnel interviewed and documents reviewed and considering findings during the inspection, which include the observations listed in the inspection report, a decision on the compliance of **[company name and address]** with WHO guidelines for the manufacture of [scope, e.g. oral solid dosage form] **will be made after the manufacturer's response to the observations has been assessed.**

The manufacturer must respond to the **final report observations** where, for each one, a description of the corrective action implemented or planned to be implemented and the target date of completion are included.

_____ Date _____

(Lead Inspector)

List of other accompanying inspectors/personnel

Sr. No.	Name	Institution	Role in the inspection

ANNEXURE III: CORRECTIVE ACTION AND PREVENTIVE ACTION (CAPA) FORMAT

AMRH logo	COMPLIANCE REPORT	Manufacturer: Address: Audit Dates: Auditors: Audit Standard: WHO GMP GUIDELINES Response date:

AMRH logo	COMPLIANCE REPORT[1]

Critical Deficiency	Manufacturer's Response	Proposed Completion Date	Auditor's comments	Response Accepted Y / N
None found during audit	Corrections to observed examples: The identified Root Cause: Corrective and Preventive Action(s) for the Root Cause: Objective Evidence Provided:			

[1] **Explanatory Notes:** The applicant must respond to all observations, under the respective classifications assigned by the auditors, noting that Root Cause analysis is not a requirement (but can be included) for observations classified as 'Other'. Responses are to be submitted within 60 days of receipt of the inspection report.

Critical Deficiency	Manufacturer's Response	Proposed Completion Date	Auditor's comments	Response Accepted Y / N
None found during audit	Corrections to observed examples: The identified Root Cause: Corrective and Preventive Action(s) for the Root Cause: Objective Evidence Provided:			
Critical Deficiency	**Manufacturer's Response Note: for other deficiencies, objective evidence is not required**	**Proposed Completion Date**	**Auditor's comments**	**Response Accepted Y / N**
	Corrections:			
	Corrections:			

Signature:_____ Date: _____

ANNEXURE IV: INSPECTION CLOSURE LETTER

1. Member States, countries that have ratified the AMA Treaty, will adopt the AMRH GMP decision.

2. In countries that have not ratified the AMA Treaty, the decision will follow national regulatory processes, or they may adopt the AMRH GMP decision if they wish.

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for GMP Compliance Status Determination

1. Policy

- Accurate records of all inspections must be maintained, including all communications with the company with respect to each inspection.
- Uniformity and consistency in the approach are required to build confidence in the initiative, and to ensure variance in inspection outcomes is purely based on the company's quality system and not operational issues within the work-sharing initiative.
- The inspection report must provide a factual and objective record of the inspection that includes what was done, the inspection findings for each activity inspected, and a conclusion that applies to the time the report is written.
- Inspection reports should be written in the third person passive style and the past tense

2. Scope

This procedure applies to the determination of the compliance status of a site by GMP inspectors under the AMRH collaboration.

3. Purpose

The purpose of this SOP is to outline the procedure for GMP inspection report writing and the follow-up of the same, for all AMRH inspections.

4. Definitions

i. AMRH Inspections coordinator- a member of the secretariat assigned to carry out the roles of coordinating the continental inspections and inspection activities.

ii. AMRH – African Medicines Regulatory Harmonisation. This term will be replaced with the African Medicines Agency once it becomes operational.

iii. AMRH GMP Technical Committee – a team of GMP experts selected from all the Regional Economic Communities (REC) of the African Union. They provide technical evaluation of the work and documents the AMRH GMP inspectorate uses.

5. Responsibility

i. All inspectors – following the procedure to document every GMP inspection

ii. AMRH GMP Inspections Coordinator – ensuring the procedure is followed every time, and that all reports and CAPAs are appropriately maintained and archived.

iii. Lead Inspector – accurate documentation of the inspection s/he had led

iv. GMP TC – active participation and input in reviewing the final inspection report and CAPA, leading to an appropriate recommendation.

6. Procedure

Whereas it is recognised that it is impossible to encompass every situation that may generate a risk, the following principles should be considered:

7.1 Classification of observations is based on the assessed risk level and number of occurrences and may vary depending on the nature of products manufactured.

7.2 A deficiency that was reported at a previous inspection and not corrected may be reported in a higher classification of observation depending on the risk to the patient.

7.3 Once-off minor lapses or less significant issues are not formally reported but are brought to the manufacturer's attention during the inspection.

7.4 All GMP inspection deficiencies will be classified using Appendix II.

7.5 After the classification of GMP observations, a final conclusion of the inspection will be reached using the decision rule below and also taking into consideration step 7.1:

Tabulated compliance determination scenarios

	Scenario	Inspection conclusion
1	Only other/minor observations	**Acceptable** level cGMP subject to an AMRH peer review mechanism CAPA to be submitted
2	Other and a few (< 6) major deficiencies:	Decision on level of compliance to be made after receipt and evaluation of CAPAs CAPA **± Re-inspection**
3	Any critical or several (≥ 6) major deficiencies	**Unacceptable** level of cGMP compliance *Depending on the critical observation, an onsite regulatory decision may have to be taken in consultation with the Inspections Coordinator and GMP TC if there is an immediate and urgent public health risk.* CAPA **± Re-inspection**

7.6 Records

7.7 Final Inspection Report

8. References

8.1 WHO Technical Report Series (TRS), No 996, Annexure 4

9. Annexures

9.1 Guide for Classification of Deficiencies

9.2 Flowchart

10. History And Authorisation

SOP Version	Date authorised	Reason for Change	Authorised by
00		New SOP	

ANNEXURE 1: GUIDE FOR CLASSIFICATION OF DEFICIENCIES

**The list is non-exhaustive. Guidance and classification may vary based on the product type, facility, evidence, and scenario quality risk assessment.*

1. Premises

a. Risk 1 (Critical) Observations

i. No air filtration system

ii. Generalised malfunctioning of the ventilation system(s)-Contamination evident.

iii. Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high-risk products such as highly sensitising drugs, biological, hormones, cytotoxic drugs or highly active drugs

iv. The design of premises does not allow unidirectional flow of material and personnel with evidence of risk of cross-contamination

b. Risk 2 (Major) Observations

i. Malfunctioning of the ventilation system could result in localised or occasional cross-contamination.

ii. Maintenance/periodic verification, such as air filter replacement and monitoring of pressure differentials is not performed.

iii. Accessory supplies (steam, air, nitrogen, dust collection, etc.) are not qualified.

iv. Heat, Ventilation, Air Conditioning (HVAC) and purified water systems are not qualified.

v. Temperature and humidity are not controlled or monitored when necessary (for example, storage not in accordance with labelling requirements).

vi. Damage (holes, cracks or peeling paint) to walls/ceilings immediately adjacent to or above manufacturing areas or equipment where the product is exposed.

vii. Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment.

viii. Surface finish (floors, walls and ceilings) that does not permit effective cleaning.

ix. Unsealed porous finish in manufacturing areas with evidence of contamination (mildew, mould, powder from previous productions, etc.).

x. Insufficient manufacturing space that could lead to mix-ups.

xi. Physical and electronic quarantine is accessible to unauthorised personnel/Physical quarantine area is not well marked and/or not respected when used.

xii. No separate area/Insufficient precautions to prevent contamination or cross-contamination during raw material sampling.

c. Risk 3 (Other) Observations

i. Doors give direct access to the exterior from manufacturing and packaging areas used by personnel.

ii. Un-screened/Un-trapped floor drains.

iii. Outlets for liquids and gases are not identified.

iv. Damage to surfaces not directly adjacent to or above exposed products.

v. Non-production activities are performed in production areas.

vi. Inadequate rest, change, wash-up and toilet facilities.

2. Equipment

a. Risk 1 (Critical) Observations

i. Equipment used for complex manufacturing operations of critical products not qualified and with evidence of malfunctioning or lack of appropriate monitoring.

b. Risk 2(Major) Observations

i. Equipment does not operate within its specifications.

ii. Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerised systems, is not qualified.

iii. Tanks for manufacturing liquids and ointments are not equipped with sanitary clamps.

iv. Stored equipment is not protected from contamination.

v. Inappropriate equipment for production: surfaces porous and non-cleanable/material sheds particles.

vi. Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment.

vii. No covers for tanks, hoppers or similar manufacturing equipment.

viii. No inadequate precautions are taken when equipment such as an oven or autoclave contains more than one product (possibility of cross-contamination or mix-ups).

ix. Equipment location does not prevent cross-contamination or possible mix-ups for operations performed in a common area.

x. Purified water system not maintained or operated to provide water of adequate quality.

xi. Leaking gaskets with potential impact on product quality.

xii. No calibration programme for automatic, mechanical, electronic or measuring equipment/no records maintained.

xiii. No preventative maintenance programme for major equipment/no records maintained.

xiv. No equipment usage logs.

c. Risk 3 (Other) Observations

i. Insufficient distance between equipment and walls to permit cleaning.

ii. Base of immovable equipment is not adequately sealed at points of contact.

iii. Use of temporary means or devices for repair.

iv. Defective or unused equipment not removed or appropriately labelled.

v. Minor equipment used for non-critical products is not qualified.

3. Personnel

a. Risk 1 (Critical) Observations

i. individual in charge of Quality Control (QC) or production for a fabricator of critical/high-risk products does not hold a university degree in a science related to the work being conducted and does not have sufficient practical experience in their responsibility area.

b. Risk 2 (Major) Observations

i. Individual in charge of QC or Production for a fabricator, packager/labeller, importer, distributor or tester does not hold a university degree in a science related to the work being conducted.

ii. Individual in charge of QC or Production for a fabricator, packager/labeller, importer, distributor or tester does not have sufficient practical experience in their responsibility area.

iii. Individual in charge of QC for a wholesaler or secondary labeller is not qualified by academic training and experience.

iv. Delegation of responsibilities for QC or Production to insufficiently qualified persons.

v. Insufficient personnel for QC or production operations results in a high error probability.

vi. Insufficient training for personnel involved in production and QC resulting in related GMP deviations

c. Risk 3 (Other) Observations

i. Inadequate training records.

ii. Insufficient written training programme

4. Sanitation

a. Risk 1 (Critical) Observations

i. Evidence of widespread accumulation of residues/ extraneous matter indicative of inadequate cleaning.

ii. Evidence of gross infestation.

b. Risk 2(Major) Observations

i. Sanitation programme is not in writing, but the premises are in an acceptable state of cleanliness.

ii. There are no standard operating procedures (SOP) for microbial/environmental monitoring and no action limits for areas where susceptible non-sterile products are manufactured.

iii. Cleaning procedures for production equipment not validated (including analytical methods).

iv. Inadequate written health requirements and/or hygiene programme.

v. Health requirements and/or hygiene programmes are not correctly implemented or followed.

c. Risk 3 (Other) Observations

i. Incomplete written sanitation procedure.

ii. Incomplete implementation of the written sanitation programme.

5. Raw Material Testing

a. Risk 1 (Critical) Observations

i. Evidence of falsification or misrepresentation of analytical results.

ii. No evidence of testing Certificate of Analysis (COA) is available from the supplier/synthesiser, and no testing is done.

b. Risk 2 (Major) Observations

i. Reduced testing programme in place without adequate certification of the vendors/suppliers.

ii. The water used in the formulation is not of acceptable quality.

iii. Insufficient testing of raw material.

iv. Incomplete specifications.

v. Specifications not approved by QC.

vi. Test methods not validated.

vii. Use of raw material after retest date without proper retesting.

viii. Use of raw material after the expiration date.

ix. Multiple lots of the same raw material, comprising one reception, are not considered as separate for sampling, testing and release.

x. No SOP for conditions of transportation and storage.

xi. Certification of brokers or wholesalers is allowed without proper documentation.

c. Risk 3 (Other) Observations

i. Lots identified for confirmatory testing used in production without QC approval.

ii. Incomplete validation of test methods.

6. Manufacturing Control

a. Risk 1 (Critical) Observations

i. No written Master Formula.

ii. Master Formula or manufacturing batch document showing gross deviations or significant calculation errors.

iii. Evidence of falsification or misrepresentation of manufacturing and packaging orders.

b. Risk 2 (Major) Observations

i. Master Formula prepared/verified by unqualified personnel.

ii. Lack of or incomplete validation studies/reports for critical manufacturing process (lack of evaluation/approval).

iii. Inadequate validation of changeover procedures.

iv. Unapproved/undocumented major changes compared to Master Production Documents.

v. Deviations from instructions during production are not documented and not approved by QC.

vi. Discrepancies in yield or reconciliation following production are not investigated.

vii. Line clearance between the production of different

products is not covered by SOP or documented.

viii. There are no regular checks for measuring devices/ no records.

ix. Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups.

x. Inadequate labelling/storage of rejected materials and products that could generate mix-ups.

xi. Upon receipt, bulk and in-process drugs, raw material and packaging material are not held in quarantine until released by QC.

xii. Labels are not adequately controlled.

xiii. Production personnel using bulk and in-process drugs, raw material and packaging material without prior authorisation by QC.

xiv. Inadequate/inaccurate labelling of bulk/in-process drugs, raw material and packaging material

xv. Raw material dispensing is not done by qualified persons, according to SOP.

xvi. Master Formula incomplete or showing inaccuracies in the processing operations.

xvii. Changes in batch size not prepared/verified by qualified personnel.

xviii. Inaccurate/incomplete information in manufacturing/packaging batch documents.

xix. Although documented, batches are combined without QC approval and/or are not covered by SOP.

xx. No written procedures for packaging operations.

xxi. Non-standard occurrences during packaging are not investigated by qualified personnel.

xxii. Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, and disposal).

xxiii. Inadequate handling of outdated/obsolete packaging material.

xxiv. No or inadequate self-inspection programme Programme does not address all applicable sections of GMPs/Records incomplete or not maintained.

xxv. Fabrication, packaging/labelling, and testing operations are carried out at a site not holding a valid manufacturing licence.

xxvi. There is no agreement between the contractor, the importer and the distributor covering the fabrication and packaging/labelling operations.

xxvii. Recall:

i. Absence of recall procedure combined with distribution practices that would not permit an adequate recall (distribution records unavailable or not kept).

ii. Improper quarantine and disposal practices that would allow recalled/rejected units to be returned for sale.

c. Risk 3 (Other) Observations

i. Incomplete SOPs for the handling of materials and products.

ii. Access to production areas is not restricted to authorised personnel.

iii. Inadequate checks for incoming materials.

iv. Written procedures incomplete for packaging operations.

v. Incomplete recall procedure.

vi. There is no agreement between the wholesaler, the importer and the distributor relative to a recall of a drug when the importer or distributor assumes the wholesaler's responsibilities with respect to recalls.

vii. Incomplete/inaccurate annual product quality review.

7. Quality Control Department

a. Risk 1 (Critical) Observations

i. No person in charge of QC is available on the premises.

ii. The quality Control department is not a distinct and independent unit, lacking real decisional power, with evidence that the production department or

management often overrules QC decisions.

b. Risk 2 (Major) Observations

i. Inadequate facilities, personnel and testing equipment.

ii. No authority to enter production areas.

iii. No SOPs approved and available for sampling, inspection and testing of materials.

iv. Products made available for sale without the approval of the QC department.

v. Products released for sale by QC without proper verification of manufacturing and packaging documentation.

vi. Master production documents not in compliance with marketing authorisation.

vii. Out-of-specification test results, deviations and borderline conformances are not properly investigated and documented, according to an SOP.

viii. Raw material/packaging material used in production without prior approval of QC.

ix. Reprocessing/Reworking is done without prior approval of the QC department.

x. Lack of or inadequate system for complaint handling.

xi. Returned goods are made available for sale without assessment and/or approval by QC.

xii. SOPs covering operations that can affect the quality of a product, such as transportation, storage, etc, are not approved by the QC department/not implemented.

xiii. There is inadequate evidence to demonstrate that storage and transportation conditions are appropriate.

xiv. Lack of or insufficient change control system.

xv. For testing laboratories (in-house or contract), the systems and controls in place for the proper qualification, operation, calibration and maintenance of equipment, standards, solutions, and records keeping do not assure that the results and conclusions generated are accurate, precise and reliable.

xvi. Products tested at a site not holding a valid GMP licence/certificate.

xvii. Sterility testing is not performed in a Grade A environment within a Grade B background or in an isolator of a Grade A within an appropriate background and limited access to non-essential personnel.

c. Risk 3 (Other) Observations

i. iThere is no agreement between the contract laboratory and the establishment covering the testing activities.

ii. Investigations of non-conformances not completed in a timely manner.

8. Packaging Material Testing

a. Risk 2 (Major) Observations

i. Reduced testing programme in place without adequate certification of vendors/suppliers.

ii. Lack of or insufficient testing of packaging material.

iii. Inadequate specifications.

iv. Specifications not approved by QC.

v. No identity test is done by the packager/labeller after receipt on its premises.

vi. Certification of brokers or wholesalers is done without proper documentation.

b. Risk 3 (Other) Observations

i. Inadequate procedures of transportation and storage.

ii. Inappropriate environment and/or precautions to prevent contamination of packaging material during sampling.

9. Finished Product Testing

a. Risk 1 (Critical) Observations

i. The finished product is not tested for compliance with applicable specifications by the importer/ distributor before release for sale, and no evidence is available that the fabricator has tested the products.

ii. Evidence of falsification or misrepresentation of testing results/forgery of COA.

b. Risk 2 (Major) Observations

i. Non-compliant products made available for sale.

ii. Incomplete/inadequate specifications.

iii. Finished product specifications not approved by QC.

iv. Incomplete testing.

v. No identity testing upon receipt at the site and/or no periodic complete confirmatory testing.

vi. Lack of or insufficient validation of test methods.

vii. No SOP for conditions of transportation and storage.

viii. Use of unique identifier principles not meeting the acceptable options.

c. Risk 3 (Other) Observations

i. Inadequate method transfer for a validated analytical method.

ii. The method validation report does not specify the revision of the analytical method used during validation.

10. Records

a. Risk 1 (Critical) Observations

i. Evidence of falsification or misrepresentation of records.

b. Risk 2 (Major) Observations

i. Lack of or incomplete Master Production Documents.

ii. Unavailability of documentation from suppliers in a timely manner.

iii. Lack of or incomplete records of sale.

iv. Lack of or incomplete records of complaints regarding the quality of a drug.

c. Risk 3 (Other) Observations

i. Incomplete plans and specifications for the manufacturing buildings

ii. Insufficient retention time for evidence and records to be maintained.

iii. No organisation charts.

iv. Incomplete records for the sanitation programme.

11. Samples

a. Risk 2 (Major) Observations

i. Retained samples are not kept for finished products.

ii. Failure to submit retained samples when alternative sample retention is granted.

b. Risk 3 (Other) Observations

i. Samples of raw materials are not available.

ii. Insufficient quantity for finished products or active pharmaceutical ingredients (API).

iii. Improper storage conditions.

12. Stability

a. Risk 1 (Critical) Observations

i. No data is available to establish the shelf-life of products.

ii. Evidence of falsification or misrepresentation of stability data/forgery of COA.

b. Risk 2 (Major) Observations

i. There is an insufficient number of lots to establish shelf-life.

ii. Insufficient data to establish shelf-life.

iii. No action is taken when data shows that the products do not meet their specifications before expiry.

iv. Lack of or inadequate continuing stability programme.

v. There are no stability studies pertaining to manufacturing (formulation)/packaging material changes.

vi. Testing methods not validated.

vii. Enrolling worst-case scenarios is not considered (for example, reworked/reprocessed lots).

viii. Inappropriate storage conditions for stability samples.

c. Risk 3 (Other) Observations

i. Stability testing is not performed at the time required by the written programme.

ii. Review of stability data not performed in a timely manner.

13. Sterile Products

a. Risk 1 (Critical) Observations

i. Lack of or inadequate validation of critical sterilisation cycles.

ii. Water for Injection (WFI) systems are not validated with evidence of problems such as microbial/ endotoxin counts not within specifications.

iii. No media fills are performed to demonstrate the validity of aseptic filling operations.

iv. No environmental controls/No monitoring for viable microorganisms during filling for aseptically filled products.

v. Aseptic filling operations continued following unsatisfactory media fill results obtained.

vi. Batches failing the initial sterility test are released for sale based on a second test without proper investigation.

vii. Environmental conditions for aseptic operations are inadequate.

viii. Absence of leak test for ampules

b. Risk 2 (Major) Observations

i. Aqueous-based products are not subject to terminal steam sterilisation without proper justification or approval through the marketing authorisation.

ii. Inadequate room classification for processing/filling operations.

iii. Aseptic manufacturing suites are under negative pressure compared to clean areas (C-D). Clean areas (C-D) under negative pressure to unclassified areas.

iv. Insufficient number of samples taken for environmental monitoring/inadequate sampling methods.

v. Insufficient environmental controls/Insufficient monitoring for viable microorganisms during filling for aseptically filled products.

vi. Premises and equipment not designed or maintained to minimise contamination/generation of particles.

vii. Inadequate maintenance of purified water and WFI systems.

viii. Inadequate re-validation of purified water and WFI systems after maintenance, upgrading, and out-of-spec trends.

ix. Inadequate training of personnel.

x. Personnel are involved in aseptic filling before completing successful media fill.

xi. Inadequate gowning practices for clean and aseptic areas.

xii. Inadequate sanitation/disinfection programme.

xiii. Inadequate practices/precautions to minimise contamination or prevent mix-ups.

xiv. Non-validated time lapse between cleaning, sterilisation, and use of components, containers and equipment.

xv. No consideration is given to bioburden before sterilisation.

xvi. Non-validated time lapse between the start of manufacturing and sterilisation or filtration.

xvii. Inadequate programme for media fill.

xviii. The capability of media to grow a broad spectrum of microorganisms is not demonstrated.

xix. Misinterpretation of results for media fill.

xx. Samples for sterility testing are insufficient in number or not representative of the entire production run.

xxi. Each steriliser load is not considered a separate lot for sterility testing.

xxii. Purified water is not used as the feed water for the WFI system and the clean steam generator.

xxiii. Inadequate testing programme for WFI.

xxiv. The WFI used for the final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and components are not depyrogenated subsequently.

xxv. Inappropriate environment/controls for crimping following aseptic filling.

xxvi. Inadequate inspection for particles and defects.

xxvii. Gases are used to purge solutions or blanket products not passed through a sterilising filter.

xxviii. Inadequate integrity testing of sterilising or vent filters.

c. Risk 3 (Other) Observations

i. Steam used for sterilisation is not monitored to ensure suitable quality.

ii. Inadequate control of the maximum number of personnel present in clean and aseptic areas.

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SOP for GMP Inspection CAPA Review and Closure

1. Policy

- The inspection process should be concluded with a decision regarding compliance with Good Manufacturing Practices, which informs the registration process for pharmaceutical products.

- Close-out of inspections must be made based on the inspection report and/or evaluation of the company's response to the inspection report. Inspections can be closed out if no corrective and/or preventive actions are required.

- Final recommendations will be made during teleconferences where each Focal Person or their designate must participate.

2. Scope

This procedure applies to all inspections for manufacturers of finished medicinal products and quality control laboratories inspected under the AMRH collaboration.

3. Purpose

The purpose of this SOP is to ensure that a standardised procedure is followed by all inspectors when closing out an inspection.

4. Definitions

i. AMRH Inspections coordinator- a member of the secretariat assigned to carry out the

ii. roles of coordinating the continental inspections and inspection activities.

iii. AMRH – African Medicines Regulatory Harmonisation. This term will be replaced with the African Medicines Agency once it becomes operational.

iv. AMRH GMP Technical Committee – a team of GMP experts selected from all the Regional Economic Communities (REC) of the African Union. They provide technical evaluation of the work and documents the AMRH GMP inspectorate uses.

5. Responsibility

i. Inspectors, particularly the Lead Inspector - evaluation of site response, corrective actions and follow-up actions.

ii. AMRH Inspections Coordinator – tracking of inspections and confirming GMP compliance status.

6. Procedure

a. Compliance Report/Corrective Action and Preventive Action (CAPA) review

i. After receipt of the compliance report, the Lead Inspector should determine which inspector will conduct the initial review and complete the relevant sections in the review template given in Annexure 1. Alternatively, they can task each inspector to conduct a review, which the Lead Inspector then evaluates and/or incorporates the review comments.

ii. During the review, attend to each deficiency, cross-referencing the cited reference, the manufacturer's response, and the submitted supporting evidence.

If satisfied that the GMP deficiency was adequately addressed, indicate this in the inspectors' comments section.

If not satisfied, clearly write down the shortcomings of the manufacturer's response to the deficiency in the inspectors' comments.

If additional information is required, the Lead Inspector must contact the company detailing what is required or why the response was not accepted, and specify a suitable timeframe by which the information is expected.

iii. Circulate the completed Compliance Review Report together with the supporting evidence to the GMP TC and/or NRA AMRH GMP

Focal Persons within **30 days** of receipt of the CAPA.

Within **seven days** of circulating the report, convene a virtual meeting of the participating inspectors and GMP TC and/or NRA AMRH GMP Focal Persons and discuss the review report.

iv. Reach a final decision on the overall recommendation regarding the inspection with the consensus of the co-inspectors and Focal Persons. Where additional information has been requested and is awaited, a final decision will be deferred until after review of the additional information.

Any additional information must be received within the agreed stipulated timeframe and, after that, be handled in the same manner as an initial submission in terms of timelines.

v. If the company has not responded to the inspection report within the specified timeframe (no corrective actions submitted), the Lead Inspector must contact the company requesting the required response within 14 days, copying the Inspections Coordinator and the co-inspectors.

vi. Where there are major observations of concern that have not been satisfactorily addressed or if the company does not submit the CAPA after the initial reminder without any request for extension, the facility will be considered non-compliant. The Inspections Coordinator will indicate in the tracking form how the recommendation was reached.

vii. The Inspections Coordinator should document the final recommendation, sign the letter and officially email it to the GMP TC.

viii. After reaching the final decision and overall recommendation, the Lead Inspector will prepare the inspection closure letter as per Annexure 2.

b. Conclusion of the inspection and communication with applicants

i. Based on the common position reached by the GMP TC,

- NRAs that have ratified the AMA Treaty will adopt the final GMP compliance decision of the AMRH inspection.

- NRAs that have not ratified the AMA Treaty will ensure that final recommendations follow the country-level process for a final GMP compliance decision.

ii. NRA Focal Persons must notify the AMRH GMP Inspections Coordinator of the final decision and its date.

7. Records

i. Compliance Review Report

8. References

i. SOP AMRH-GMP-004 Inspection Reporting

ii. WHO Technical Report Series (TRS), No. 986 of 2014

9. Annexes

i. Annexure 1: Compliance Review Report

ii. Annexure 2: Inspection closure letter

iii. Annexure 3: Flowchart

10. History and Authorisation

SOP Version	Date authorised	Reason for Change	Authorised by
00		New SOP	

ANNEXURE 1: COMPLIANCE REPORT FORMAT

AMRH logo	COMPLIANCE REPORT	Manufacturer: Address: Audit Dates: Auditors: Audit Standard: WHO GMP GUIDELINES Response date:

AMRH logo	COMPLIANCE REPORT[1]

Critical Deficiency	Manufacturer's Response	Proposed Completion Date	Auditor's comments	Response Accepted Y / N
None found during audit	Corrections to observed examples: The identified Root Cause: Corrective and Preventive Action(s) for the Root Cause: Objective Evidence Provided:			

[1] **Explanatory Notes:** The applicant must respond to all observations, under the respective classifications assigned by the auditors, noting that Root Cause analysis is not a requirement (but can be included) for observations classified as 'Other'. Responses are to be submitted within 60 days of receipt of the inspection report.

Major Deficiency	Manufacturer's Response	Proposed Completion Date	Auditor's comments	Response Accepted Y / N
None found during audit	Corrections to observed examples: The identified Root Cause: Corrective and Preventive Action(s) for the Root Cause: Objective Evidence Provided:			
Other Deficiency	**Manufacturer's Response Note: for other deficiencies, objective evidence is not required**	**Proposed Completion Date**	**Auditor's comments**	**Response Accepted Y / N**
	Corrections:			
	Corrections:			

Signature:_____ Date: _____

ANNEXURE 2: INSPECTION CLOSURE LETTER

Tel:

Email:

Enquiries:

Reference:

Responsible Pharmacist/Person:

Site Name:
Site Address:

Tel:

Tel:

Email:

Dear [Responsible Pharmacist/person],

Re: AMRH RESOLUTION IN TERMS OF THE INSPECTION CONDUCTED AT [MANUFACTURER'S NAME] – BUILDING/UNIT/WORKSOP/SUITE AS DESCRIBED IN SITE MATER FILE [SMF NUMBER] EDITION: [SMF EDITION NUMBER], EFFECTIVE DATE: [SMF EFFECTIVE DATE]

The inspection report and your subsequent responses for the (Remote) Inspection of [Manufacturer's name] located at [manufacturer's site address] conducted by the AMRH Inspection team represented by [inspectors' names] on [inspection dates]to verify compliance with current Good Manufacturing Practices (cGMP) refers.

It is confirmed that the inspection covered the following areas only:

After the inspection, the following resolutions were made:

1. GMP Status

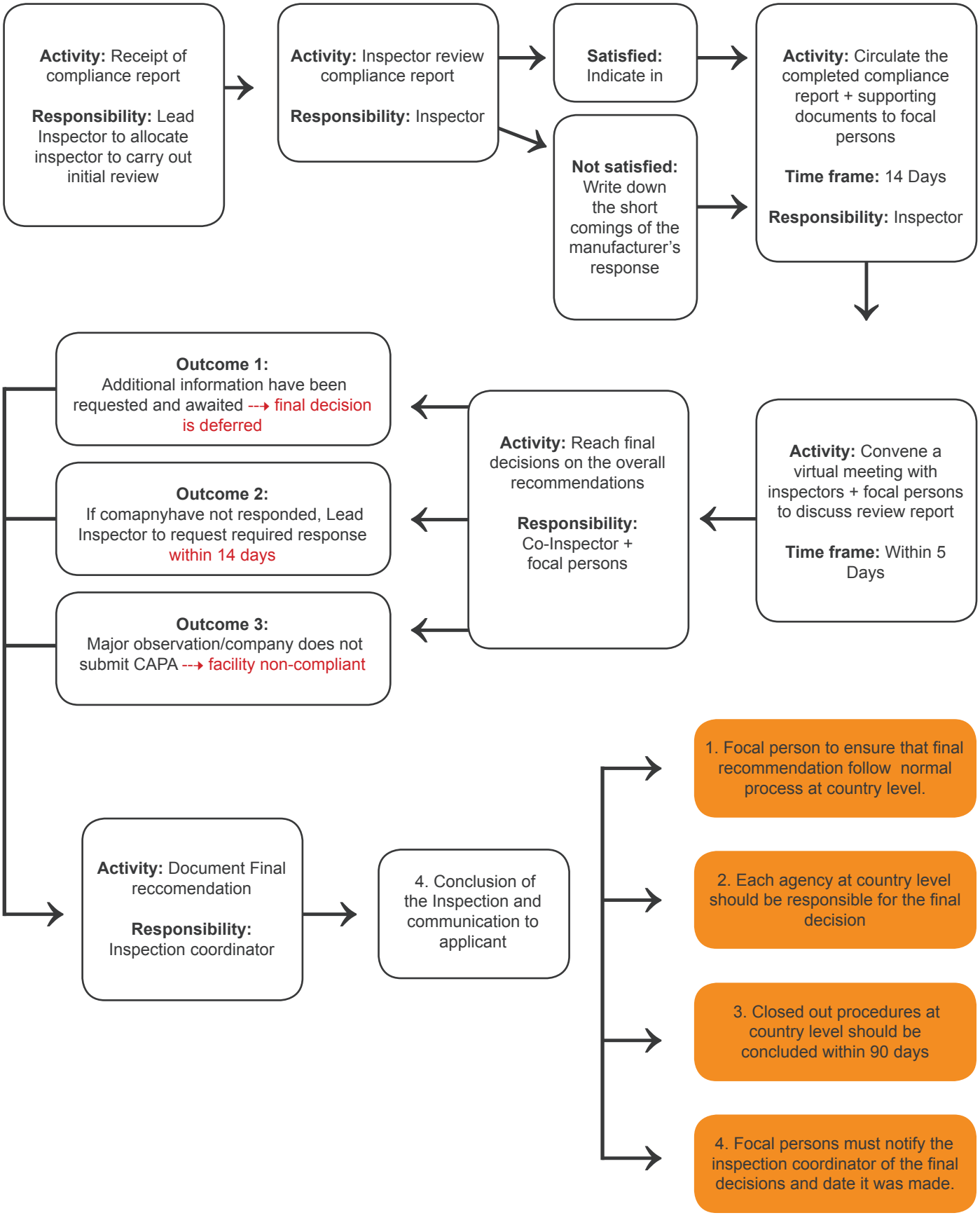
Based on the areas inspected, the people met, and the documents reviewed; and considering the findings and the deficiencies listed in the inspection report, and the company's responses dated [CAPA response date], the manufacturer, [manufacturer's name], **was found to be operating at an acceptable/non-acceptable level of compliance** with the AMRH principles and guidelines for Good Manufacturing Practice of pharmaceutical/ biological and medical products.

2. Validity

The resolution reflects the status of the manufacturer at the time of inspection. A re-inspection of the facility will be conducted **[insert validity period]** months from the date of this letter, at which time commitments made in the company's responses will be verified.

This letter does not constitute a GMP certificate or licence. AMRH Member States may, however, choose to issue a GMP certificate/licence based on the inspection conducted and the resolutions made. The authenticity of this letter can be verified with the issuing authority or the AMRH GMP Technical Committee.

Yours faithfully


Activity: Receipt of compliance report
Responsibility: Lead Inspector to allocate inspector to carry out initial review
Activity: Inspector review compliance report
Responsibility: Inspector
Satisfied: Indicate in
Not satisfied: Write down the short comings of the manufacturer's response
Activity: Circulate the completed compliance report + supporting documents to focal persons
Time frame: 14 Days
Responsibility: Inspector
Activity: Convene a virtual meeting with inspectors + focal persons to discuss review report
Time frame: Within 5 Days
Activity: Reach final decisions on the overall recommendations
Responsibility: Co-Inspector + focal persons
Outcome 1: Additional information have been requested and awaited --→ final decision is deferred
Outcome 2: If comapnyhave not responded, Lead Inspector to request required response within 14 days
Outcome 3: Major observation/company does not submit CAPA --→ facility non-compliant
Activity: Document Final reccomendation
Responsibility: Inspection coordinator
4. Conclusion of the Inspection and communication to applicant
1. Focal person to ensure that final recommendation follow normal process at country level.
2. Each agency at country level should be responsible for the final decision
3. Closed out procedures at country level should be concluded within 90 days
4. Focal persons must notify the inspection coordinator of the final decisions and date it was made.

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SOP for GMP Desk Review and Clearance

1. Policy

i. The procedure exists to reduce duplication of work and to ensure efficient utilisation of the limited resources through desk review of inspection reports in certain cases in lieu of on-site GMP inspections.

ii. The designated Inspector may also request additional documents to assess GMP compliance during the desk review process.

iii. Desk review approval is valid for two (2) years, provided that the validity will also be synchronised with the validity of GMP status on which the approval was based and without any detection of practices which may affect the manufacturer's credibility during this period.

iv. In case of detection of practices which affect the credibility of data submitted and the manufacturing practice, an on-site inspection will be conducted.

NB: submission of falsified information will result in potential blacklisting of the manufacturer from the AMRH processes.

2. Scope

2.1 This procedure applies to finished product manufacturers (including pharmaceutical products, biological products, vaccines, medical supplies and kites) that should be subjected to AMRH inspections to support product registrations under the collaborative initiative. It guides the desk review of inspection reports and related documents in possible lieu of an AMRH on-site inspection.

2.2 The procedure applies to facilities that are regularly (within the last two-year cycle) inspected by WLAs/SRAs, WHO pre-qualification team (WHO PQT) and AMRH member states who lead AMRH inspections and PIC/s on a case-to-case basis.

***The AMRH programme reserves the right to conduct on-site inspections of all facilities it deems necessary.**

3. Purpose

The purpose of this procedure is to outline the process for desk GMP clearance in lieu of an AMRH on-site inspection.

4. Definitions

WHO Listed Authorities (WLAs)/Stringent Regulatory Authority - The medicines regulatory authority in a country which is:

a. A member of the International Conference on Harmonisation (ICH), European Union (EU), Japan and the United States of America; or

b. An ICH Observer, being the European Free Trade Association (EFTA) as represented by Swissmedic and Health Canada (as may be updated from time to time), or

c. A regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time) and

d. Only in relation to current Good Manufacturing Practices (GMP) inspections-a medicine regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme

5. Responsibility

i. AMRH Inspections Coordinator –

- Identifies the manufacturing sites requiring GMP clearance, communicates with the company to submit the necessary documents, performs the assessment and ensures quality control of the entire process.

- Assigns the first and second reviewers and monitors timelines

ii. First Reviewer -Carries out the desk review within stipulated timelines and furnishes the port to the second reviewer.

iii. Second Reviewer – review the GMP desk clearance report.

6. Procedure

6.1 Identification of Eligible Manufacturing Sites

6.1.1 Where possible, desk reviews will only be applied after an initial physical AMRH GMP inspection.

6.1.2 All sites for finished pharmaceutical products inspected by WHO Listed Authorities (WLAs)/ Stringent Regulatory Authorities, SRAs and Pre-qualification team) PQT are eligible for desk review if they meet 6.1.2 above.

6.1.3 GMP approval can be granted following the desk review process for sites subjected to an initial AMRH on-site inspection and granted maximum validity.

6.1.4 Desk review will only be applied a maximum of two consecutive times. An on-site verification inspection will be conducted after that.

6.1.5 The AMRH inspection team reserves the right to inspect any manufacturer, irrespective of the documentary GMP evidence submitted to the AMRH.

6.2 Communication with Applicant

6.2.1 The Inspections Coordinator will request formal completion of the application form given in Annexure 1.

6.2.2 Upon receipt of a completed application form, the Inspections Coordinator will issue a proforma invoice to the applicant and request for proof of payment (PoP)

6.2.3 The Inspections Coordinator will further request documents required for desk review as per template in **Annexure 2.**

6.2.4 Requested documents should be submitted within twenty-one (21) calendar days.

6.2.5 The Inspections Coordinator will finally hand over all documents to the assigned inspectors and indicate the date relevant tracking tool.

6.3 Review of Documents

6.3.1 Upon receipt of the requested documents, the Lead Inspector/desk reviewer should assess the completeness of the application and communicate any missing requirements or further documents to the applicant within seven days, ensuring that the communication is copied to the AMRH Inspections coordinator.

6.3.2 The AMRH Inspections Coordinator will appoint the first and second (Level III inspector) reviewers, both of whom should be recipients of product applications under consideration within five days of receiving the required documents. This information will be included in the GMP tracking database.

6.3.3 The Inspector assigned to review first should finish his review within 30 calendar days (1 month) from the receipt of the required documents. If this is not possible, the Inspector assigned to review should notify the AMRH Inspections Coordinator well before this timeline so that the desk assessment can be reassigned.

6.3.4 The submitted documents should all be reviewed as detailed in the following sections;

6.3.5 Check for a copy of the manufacturing authorisation for the site under consideration, granted by the local authorities, with a certified translation where the original is not in English.

6.3.6 Review of site master file and the most recent SMF in accordance with the *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14,*

6.3.7 Review coloured printouts of the Water Treatment Plant, schematic drawings of man and material movement, Air Handling Systems and pipeline and instrumentation drawings.

6.3.8 Check if the list of products (medicinal or other) manufactured on the site includes products under consideration and if there are no hazardous substances manufactured together with other products.

6.3.9 Evaluate the last inspection report and review if all relevant areas of GMP were covered durin the inspection and if the GMP standard is equivalent to current WHO GMP guidelines. Where the inspection report is not in English, a copy must be submitted with a certified translated copy.

6.3.10 Evaluate the adequacy of the CAPAs and proof of CAPAs implementation related to the last inspection report observations/deficiencies or any warning letter or equivalent regulatory action.

6.3.11 Review the inspection closure letter or equivalent documentation. Where the closure letter is not in English, a copy must be submitted together with a certified translated copy.

6.3.12 Review the SOP and most recent PQR(s) of the concerned product(s) as selected based on risk management principles. PQR should be reviewed in line with, (WHO Good Manufacturing Practices: main principles for pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eighth Report Geneva,* World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2), or the latest applicable technical report series.

6.3.13 Review the SOP for the purified water system and the most recent Purified Water System Review in line with, (WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva,* World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2).

6.3.14 Ensure the availability of a confirmation by the senior QA representative that a full external audit dedicated to the product(s) has been performed and all matters dealt with.

6.3.15 Review the last three completed batch manufacturing/packaging record(s), including the analytical part for the most recently released batch of relevant product(s) as selected based on risk management principles

6.3.16 Review the SOP and recall reports of any recalls in the last three years. Where no recall was conducted, review the most recent mock recall report.

6.3.17 Review the annual product quality review reports.

6.3.18 Trend analysis of environmental monitoring, especially in case sterile product for last year

***A hybrid inspection approach may be explored by requesting a virtual connection to clarify any areas, documents or practice**

6.4 Reporting

6.4.1 After reviewing and evaluating the documents mentioned above - prepare a desk review report per the template in **Annexure 3** and submit it to the second reviewer within 30 calendar days of all documents and proof of payment.

6.4.2 The first reviewer should indicate points to be communicated to the manufacturer in red, bold and highlighted in yellow as follows: **xxxx**. Each shortcoming must reference the relevant section in the WHO GMP guidelines.

6.4.3 The first reviewer should copy the questions/ observations raised in the report into the 'points to be communicated to the manufacturer's section at the beginning of the report (within 15 days of starting the review).

6.4.4 The second reviewer should review and verify source documents where necessary and incorporate comments within fifteen (15) calendar days of receiving the initial report from the first reviewer.

6.4.5 The second reviewer's comments should be in blue and bolded. Additional points should be communicated to the manufacturer in blue, bold and highlighted in yellow as follows: **xxxx**.

6.4.6 The second reviewer is responsible for editing these questions for clarity and finalising the questions for the manufacturer. These questions should be written and addressed to the manufacturer such that they will be copied straight into a letter

6.4.7 After incorporating points from the second reviewer, circulate the desk review report and arrange a plenary for final review.

6.4.8 Where final review is through telephone conference the same must be held within fifteen (15) days while for a physical meeting, report should be tabled in the next meeting

6.5 Decision Making Process

6.5.1 Following review and discussion at the GMP TC and if the submitted documentation are not acceptable, the manufacturer should be informed of the decision to conduct an on-site inspection citing the major reasons.

6.5.2 For generally acceptable sites, the lead GMP inspector will dispatch the raised queries to the manufacturer. The query responses should be submitted within fourteen (14) days, failure to which inspection should be closed.

6.5.3 Upon receipt of query responses, send to the original first reviewer to review the responses using the template in annexure 3, submit to second reviewer and seek comments and endorsement from GMP TC persons within ten (10) days of receiving the query response.

6.5.4 The Lead Inspector will send the closure letter to the Inspections Coordinator as per template in annexure

6.5.5 Based on the common position reached by the GMP TC,

a. NRAs that have ratified the AMA Treaty will adopt the final GMP compliance decision of the AMRH inspection.

b. NRAs that have not ratified the AMA Treaty will ensure that final recommendations follow the normal process at country level for a final GMP compliance decision.

c. NRA Focal Persons must notify the AMRH GMP Inspections Coordinator of the final decision and the date it was made.

7. Records

The following documents will be generated from the assessment:

i. GMP desk clearance report, query letter and final outcome letter

8. References

i. WHO Technical Report Series, No. 986, 2014, Annex 2.

ii. WHO Technical Report Series, No. 970, 2012, Annex 2.

iii. WHO Technical Report Series, No. 961, 2011, Annex 14.

iv. WHO Technical Report Series, No. 961, 2011, Annex 10.

9. Annexes

i. Annexure 1: Application form

ii. Annexure 2: Letter requesting documents for GMP desk clearance

iii. Annexure 3: GMP Desk Clearance report

iv. Annexure 4: Response to query template

v. Annexure 5: Closure letter

vi. Annexure 6: Flowchart

10. History and Authorisation

SOP Version	Date authorised	Reason for Change	Authorised by
00		New SOP	

ANNEXURE 1: APPLICATION FORM

ANNEXURE 2: LETTER REQUESTING DOCUMENTS FOR GMP DESK CLEARANCE

REF: ……

Date

Facility Address

Dear Sir/Madam,

RE: DOCUMENTS REQUIRED FOR DESK REVIEW: *Facility Address*

Reference is made to the products from the above-mentioned premises that are under evaluation for registration under the AMRH collaboration initiative. Confirmation of cGMP compliance is a pre-requisite for the approval of all products. In that regard, please be advised that inspectors from the region would like to carry out a desk review for GMP compliance of your premises as part of the assessment for the registration of **xxxx (names of products).**

To facilitate the GMP desk clearance of your site, kindly provide us with a full set of the following documents in English

1. A copy of the manufacturing authorisation granted by the local medicines regulatory authority
2. An updated SMF that is not older than one year from its approval date and any forecasted modifications, including:
3. Legible coloured printouts of Water Treatment Plant, schematic drawings of man and material movement, Air Handling Systems, including pipeline and instrumentation drawings (P& I Ds).
4. A list of all the products (medicinal or other) manufactured on site. The list should include proprietary names and INN;
5. A copy of the most recent two inspection reports (not older than 2 years) of an inspection conducted by a WHO Listed Authority (WLA)/Stringent Regulatory Authorities with a certified translated copy where this is not in English and, if relevant, GMP certificates arising from these inspections with a certified translated copy where this is not in English. Please note that the scope of the most recent on-site inspection must have included the product under consideration
6. CAPAs and proof of CAPAs implementation related to the last inspection report observations/deficiencies or any warning letter or equivalent regulatory action;
7. Reviewed CAPA from the last inspection report referred to in point 6 above
8. A copy of any warning letter or equivalent regulatory action issued by any authority to which the site provides or has applied to provide a product;
9. PQR SOP and PQR(s) **xxx (name of product within our jurisdiction for the last two years);**
10. A confirmation by the senior QA representative /authorised person that a full inspection that included products under review was performed and all matters dealt with;

11. SOP for preparing the purified water system and your internal purified water system review covering all required subsections and trend results;

12. Completed i.e. executed batch manufacturing/packaging record(s) including the analytical reports for the last three commercial production batches.

13. Recall SOP and list of any recalls in the last three years and accompanying reports or mock recall report and;

14. Validation Master Plan

15. Last Product quality annual review

16. Trend analysis for environmental monitoring especially sterile product

After review of the above-mentioned documents and any other documents that may be requested during the review, you will be informed of our decision which may be a GMP clearance or to conduct an on-site GMP inspection **(Within a month of completing the required documents).** Kindly note that the desk review report will be shared to the AMRH GMP TC, and potentially with other AMRH MemberStates.

Please note that the requested documents should be submitted electronically as email attachments and additionally on one pen drive.

Kindly confirm acceptance to submit the requested documents, by the [date, which should be within 14 days of the letter] and proof of payment of desk clearance fees at your earliest convenience, by the [date]

Signed by Head of Inspection or Designate

ANNEXURE 3: GMP DESK CLEARANCE REPORT

AMRH REPORT OF DESK-REVIEW OF GMP COMPLIANCE: Finished

Product Manufacturer:

Points for Communication to the Manufacturer

Deficiency observed	Ref

Part 1: General information

Name of the audited company	
Unit and /Block	
Physical address	
Contact person and email address.	
Product information name /conc / dosage form /pack size	
Date of review	
Summary of the activities performed by the manufacturer	
Dosage forms covered by the desk review	
Product file numbers covered by the review	
First Reviewer	
Second Reviewer	

Part 2: Summary

Part 1: General information

SMF Reference number and date			
History of AMRH inspections and compliance status			
Any specific recommendations for inspections from Assessors			
Evidence of GMP submitted in lieu of AMRH site inspection	**Name of Inspecting agency**	**Dates of inspection**	**CAPAs: (Yes/No/NA)**

Part 2: Summary of evaluation of evidence of GMP submitted in lieu of AMRH site inspection

(To be completed for each relevant inspection)

Name of inspecting agency		
Dates of inspection		
Type of inspection	**Preregistration/Routine/Follow up/Special**	
Scope of inspection:	**Unit and /Block:**	
	Production lines:	
	Dosage forms:	
	Products:	
A summary of major areas of deficiency observed		
Appropriateness of CAPAs		
Conclusion of the inspection report		
Comments/observations on the scope and comprehensiveness of the report and appropriateness of the CAPAs		
Additional documents reviewed		
Copy of the manufacturing authorisation granted by local authorities		
Review of SMF		
Schematic Drawings of Purified Water Plant, man and material movement, pressure zoning, room classification, Air Handling		
Systems		

List of all the products (medicinal or either) manufactured on site	
Copy of the last inspection report and if relevant GMP certificates coming from these inspections	
CAPAs related to the last inspection report observations/deficiencies	
PQR(s) of the concerned product(s)	
A confirmation by the senior QA representative that a full WLA/SRA audit covering the product(s) has been performed and all matters dealt with	
Master batch manufacturing/packaging record(s) and completed batch manufacturing/packaging record(s) for the most recent released batch of relevant product(s)	
Validation Master Plan	
Review of Purified Water System	
A list of any recalls in the last three years and corresponding reports or mock recall report	
Last Product quality annual review	
Trend analysis of environmental monitoring at last year	

Part 3: Conclusion

Based on the desk top review of the inspection report and considering the findings of the inspection, performed on (Date), and reflected in the observations listed in the inspection report, and the company responses, the AMRH Inspectorate is satisfied that the manufacturer, (indicate manufacturers name and location) is operating at an acceptable/unacceptable level of compliance with AMRH Good Manufacturing Practice principles and guidelines.

Products: Registration of products (indicate the name, dosage and range) manufactured at (name of the facility) will be recommended by the AMRH Inspectorate in terms of quality.

GENERAL CONDITIONS:

In addition to the aforementioned, the following condition(s) apply:

- The manufacturer to comply with WHO GMP principles,

First Review

Name…… NMRA…….

Date……

Second Review

Name…… NMRA…….

Date……

OR

In a case whereby the AMRH Inspectorate are evaluating the desktop review

Reviewers

- Must be the rapporteur
- Must be the scriber
- Other reviewers from the region

ANNEXURE 4: RESPONSE TO QUERIES

DESK GMP COMPLIANCE ASSESSMENT: RESPONSE TEMPLATE

Name of Manufacturer…….

Physical address……

SN	Query	Manufacturer's response	Reviewer's comments
1			
2			
3			
4			

Conclusion
……
……
……

First Reviewer

Name…… NMRA…….

Date……

Second reviewer

Name…… NMRA…….

Date……

ANNEXURE 5: CLOSURE LETTER

REF: …

Date

Site Name Site address

Attention: Contact person

Dear Sir/Madam

RE: Desk review of (site name)

We refer to the process of desk review undertaken following receipt of the documents submitted to support assessment of GMP compliance of the above-mentioned site.

The summary of the desk review report was tabled at the XXX meeting of the EMP TC held on the **XXXX (DATE).** We would like to inform you that the documents submitted for the desk review were assessed by the inspectors and were found to be satisfactory and considered to constitute adequate evidence of compliance with Good Manufacturing Practices. Therefore, we would like to inform you *(inspectors should select appropriate from the following):*

- That an on-site inspection by an AMRH inspection team is be waived for a maximum of two (2) years from the date of this letter

- That an on-site inspection by an [AMRH] inspection team will not be carried out at this time.

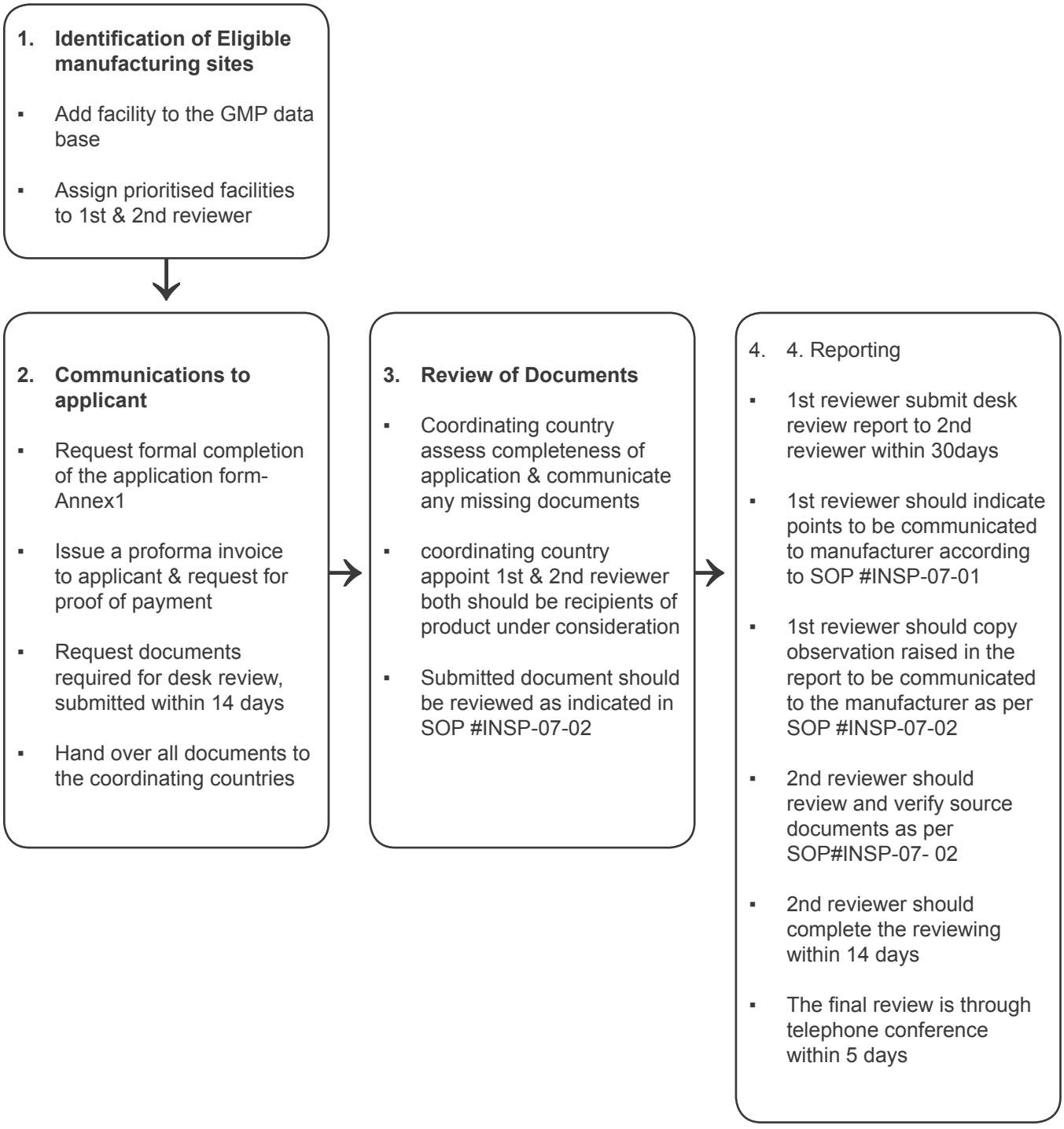
However, we would like to remind you that it remains the prerogative of AMRH Inspection team to carry out an inspection any time prior to that. It is a condition of this status that you continue to comply with WHO GMP and that you immediately bring to our notice any issue or information that might lead us to reconsider your status.

Please do not hesitate to contact the under signed should you require any further information.

Yours faithfully

Signed by Head of Inspection or Designate

ANNEXURE 6: GMP DESK CLEARANCE FLOWCHART



AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

SOP for AMRH GMP Inspections Activities Tracking

1. Policy

The various activities constituting the inspection process will be tracked to monitor progress, and to highlight any bottlenecks and administrative challenges.

Tracking information will be used to facilitate system improvement.

The Inspections Coordinator will be the focal point for the tracking and follow-up of actions.

2. Scope

This procedure applies to the major steps in the planning, performance and monitoring of inspection progress until the final decision.

3. Purpose

- This SOP aims to define the parameters to be monitored and ensure that a standardised procedure is followed in tracking AMRH inspections and availing statistics.
- To detect the bottlenecks of the inspection process, from planning to closing, and improve them.
- To monitor the performance of stakeholders in the inspection process

4. Definitions

i. *Per diem* – travel and subsistence allowance.

ii. Interim inspection report – a summary of the inspection observations, not necessarily referenced and issued to the inspected site as soon as possible at the close out of the inspection or within a week.

5. Responsibility

i. Inspections Coordinator – collecting and entering the tracking data

ii. Inspectors – confirming completion dates for each of the parameters being tracked

6. Procedure

i. The AMRH Inspections Coordinator will gather and collect the following dates and information:

- receipt of the approved itinerary
- receipt of inspectors' passport copies and bank details
- request for per diem transfers
- issuance of tickets and travel insurance

ii. The Inspections Coordinator will collect information from the inspectors for the following dates:

- issuance of Notices of Inspection
- conduct of the inspections
- issuance of Interim Inspection Report
- issuance of Final Inspection Report
- receipt of the Corrective Actions and Preventive Actions (CAPA)
- circulation of the CAPA Review Report
- teleconference to determine the final recommendation
- communication of final recommendation
- close out of inspection at country level

iii. Using the collected information, the Inspections Coordinator will maintain the statistics table showing the details of the premises inspected, the GMP status for each, and the statistics table showing the timelines for each inspection.

iv. The statistics will be tabled at every Heads of Agency meeting.

7. Records

i. Tracking table for premises inspected

ii. Tracking table for GMP inspection timelines

8. References

N/A

9. Annexes

i. Flowchart

SOP Version	Date authorised	Reason for Change	Authorised by
00		New SOP	

Tracking table for GMP inspection timelines

	Mission	Responsible personnel	Theoretical time	Actual time	Comment
1	Receipt of the approved itinerary				
2	Receipt of inspectors' passport copies and bank details				
3	Request for per diem transfers				
4	Issuance of tickets and travel insurance				
5	Issuance of Notices of Inspection				
6	Conduct of the inspections				
7	Issuance of Interim Inspection Report				
8	Issuance of Final Inspection Report				
9	Receipt of the Corrective Actions and Preventive Actions				
10	Circulation of the CAPA Review Report				
11	Teleconference to determine a final recommendation				
12	Communication of final recommendation				
13	Close out of inspection at country level				

ANNEXURE 1: MONITORING OF INSPECTION ACTIVITIES

The Inspections Coordinator will collect information from the administrative secretaries for the following dates:

- receipt of the approved itinerary
- receipt of inspectors' passport copies and bank details
- request for *per diem* transfers
- issuance of tickets and travel insurance

↓

The Inspections Coordinator will collect information from the inspectors for the following dates:

- issuance of Notices of Inspection
- conduct of the inspections
- issuance of Interim Inspection Report
- issuance of Final Inspection Report
- receipt of the Corrective Actions and Preventive Actions (CAPA)
- circulation of the CAPA Review Report
- teleconference to determine final recommendation
- communication of final recommendation
- close out of inspection at country level

↓

The Inspections Coordinator will use the collected information to maintain the table of statistics giving the following:

- the details of the premises inspected
- the GMP status for each
- the timelines for each inspection.

↓

The statistics will be tabled at every Heads of Agency meeting.

AFRICAN MEDICINES REGULATORY HARMONISATION,
AMRH GMP INSPECTIONS

SOPs and Guidelines

Inspector's Playbook

AUDA-NEPAD
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African Union

World Health Organization