Palestinian National Authority
Ministry of Health

General Directorate of Pharmacy
Drug Control and Registration Dept

Guidelines for GMP Inspection of Pharmaceutical Manufacturers

DC 001-0 **December 2007**

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A Message from

His Excellency the

Minister of Health

Dr. Fathi Abu Moghli

كلمة معالي وزير الصحة الدكتور فتحي أبو مغلي

Palestinian National Authority
Ministry of Health

Dear Colleagues,,

I have the pleasure to introduce the first Good Manufacturing Practices Inspection manual of the Palestinian Ministry of Health. This manual will be of great benefit to the Ministry of Health GMP Inspectors and to the Palestinian Pharmaceutical Manufacturers.

This manual with all supporting procedures was developed by the Department of Drug Control and Registration Staff with the support of World Health Organization (WHO).

This initiative is meant to assure the safety, efficacy and quality of pharmaceutical products used in Palestine.

I hope this manual will form an important step towards building a Palestinian health quality care system.

Sincerely

Dr. Fathi Abu Moghli

Acknowledgment

The Palestinian " Good Manufacturing Practices Inspection Guidelines were prepared by the Palestine Ministry of Health Department Drug Control and Registration Director, Chemical Engineer Mohammad Mahareeq with the assistance of staff, Pharmacist Majdi Abu-Hasan, and Ms. Jamila Wasfi.

This work was supported by the World Health Organization (WHO) and reviewed by Mrs. Edel Fitzmaurice from E. Fitzmaurice and Associates Ireland and Dr. Allen Parks from Pharmaceutical Services Corporation, USA.

1. Introduction:

This document (here and after referred to as “Guidelines for GMP inspection of pharmaceutical manufacturers”) serves as an inspection guidelines on manufacturer of pharmaceutical products. It is prepared according to World Health Organization (WHO) guidelines. This document is intended to be used by the Ministry of Health Drug Control Inspectors to assist them in assessing manufacturer’s compliance with regards to Good Manufacturing Practices (GMP). The goal of this manual is to ensure the performance of in-depth GMP audits which will enable the Ministry of Health to maintain an effective enforcement program, minimizing the consumers' exposure to adulterated and misbranded pharmaceutical products.

The manufacture and Control of Pharmaceutical Products for human and veterinary drugs is regulated by the Directorate of Pharmacy of the Palestinian Ministry of Health. The organizational unit with the authority and responsibility for compliance and enforcement of Good Manufacturing Practices regulations is the Department of Drug Control and Registration (DDCR).

Drug inspectors shall be suitably qualified in technical fields (Pharmacy, Chemistry, Microbiology, Chemical, and Engineering) at least with first university degree (B.sc), and with experience in pharmaceutical production and control. Inspections, Investigations and Regulatory follow-up are made:

- To determine whether inspected firms are operating in compliance with GMP requirements according to current guidelines of the WHO.
- To provide evidence for actions, where firms are not in compliance, to prevent adulterated products from entering the market and remove adulterated products from the market.

2. Objectives:

- This manual represents a continuing compliance and surveillance activity conducted to ensure that pharmaceutical products are prepared incompliance with GMP guidelines and their safety, efficacy and quality is assured.
- It provides inspectional guidance to investigators assigned to perform inspections of manufacturers producing pharmaceutical products and provides administration/regulatory guidance for Drug Inspectors.
- It provides information necessary to inspect overall operation of manufacturing, quality assurance, quality control, facilities and utilities, and ensures that appropriate enforcement actions are initiated against non-compliance firms.
- Continued inspections will safeguard the public health by reducing the risk of adulterated or misbranded products reaching the marketplace and increase communication between the industry and the regulatory agency.
- This manual shall be used primarily for inspecting local manufacturers and may be used for inspecting foreign manufacturers as well.

3. Scope:

The scope of the activities covered by this manual includes:

- All marketed human pharmaceutical drug products including controlled drugs.
- All marketed veterinary drug products.
- All marketed active pharmaceutical ingredients (APIs).
- All marketed cosmetic products.
- Pre-market approval for new drug where it is determined that there is a need for inspection.
- Approval for initiation of manufacturing of any of the above products in a new facility, line of production or site.
- Packaging and control for all dosage forms, including contract operations.
- Analytical control laboratories including public and private laboratories.
- This manual is not intended to be all encompassing document, rather to provide an overview of and guidance for the inspection process. This manual is not binding on the Ministry of Health but serves as guideline. Alternative methods and procedures are acceptable.

4. Standards:

Manufacturing facilities shall be inspected for GMP using the following WHO standards:

- Good Manufacturing Practices for sterile products, 2002, 36th Report;
- Guidelines on packaging for pharmaceutical products,2002, 36th Report;
- Guidance to good storage practices for pharmaceuticals, 2003, 37th Report;
- GMP for Pharmaceutical products main principles, 2003, 37th Report;
- Guidelines for sampling of pharmaceutical products and related materials , 2005, 39th Report;
- Good Manufacturing Practices: Water for pharmaceutical use, 2005 39th Report;
- GDP for Pharmaceutical Products, 2006, 40th Report;
- Supplemental Guidelines on GMP for Validation, 2006, 40th Report;
- Supplemental Guidelines on GMP for Herbal medicines, 2006, 40th Report;
- Supplemental Guidelines on GMP for HVAC for non sterile products, 2006, 40th Report.

Additional updated references may be used.

5. Personnel:

The overall responsibility for supervision and inspection of pharmaceuticals facilities is with the Director General of Pharmacy Department in the Ministry of Health.

The responsibility of the day to day inspection and follow up activities is with the Director of the Department of Drug control and Registration (DDCR) of the Ministry of Health. The GMP inspectorate is an integral part of the (DDCR) and the department director.

Licensing of pharmaceutical manufacturing premises in Palestinian National Authority falls under the auspices of the Directorate of Licensing Unit in the Ministry of Health, which provides a license to operate a business in accordance with national laws and regulations. The approval to construct a pharmaceutical plant is only granted after receipt of pre-approval from the Department of Drug Control and Registration. Such pre-approval is dependent mainly on submission of approved engineering plans of the facility.

Minimum education requirements of the GMP Inspectors is a first level degree in a scientific or engineering discipline.

The minimum training for inspectors includes:

- In-post training: should include an element of apprenticeship gained by accompanying experienced inspectors on the site visits as well as participation in courses and seminars on relevant subjects.
- Update their knowledge, for example in pharmaceutical and information technology, microbiology, and statistical aspects of quality control.

Key Responsibilities of GMP inspectors include:

- Assessing GMP compliance including irregularities and discrepancies;
- Documenting a detailed audit reports .
- Advising on improving processes and controls, which serves the public interest and ensuring the quality, safety and efficacy of pharmaceutical products.

Key Personal attributes:

- Conforms to codes of ethics and conduct.
- Independence/no conflict of interest
- Does not act as a private consultant, except in the instances of external consultants.
- Remain objective.
- Maintain confidentiality and do not provide to others the information they have obtained about the companies they have inspected.
- Communication skills including language and body language.

6. Administrative structure:

The structure, membership and operation of the GMP inspectorate is such that impartiality is safeguarded.

The national inspection services is responsible for ensuring that the requirements of the relevant national legislations are satisfied.

All personnel employed or used by the GMP inspectorate, including outside inspectors or subcontracted personnel, are not subject to any commercial, financial or other pressures which might affect their judgement. They

are not under the control of pharmaceutical manufacturers, that are assessed and licensed by the DDCR.

The system for obtaining fees does not improperly influence the inspection Procedure as finance to the DDCR Department is allocated from the Ministry of Health.

7. Code of ethics and confidentiality:

All employees shall declare if they have a conflict of interest in a company being inspected or any application for product registration.

Inspectors shall not inspect a company in which they have been a full time employee for a period of three years from leaving full time employment. An external consultant shall not have been employed for a period greater than 50 days over the past two years or 30 days in the preceding 12 months in the facility being inspected.

Inspectors and assessors shall treat with confidentiality and shall not disclose by any means, any trade, financial and confidential information gained from visits or registration documentation.

The confidential information should not be used for any other purpose than site or product evaluation.

The confidential information shall not be disclosed or provided to any person who is not bound by similar obligations of confidentiality and non use as covered by this code of ethics and conduct.

Department employees shall not accept special gifts or monetary compensation that may be offered by interested companies.

During site visits, excessive entertainment is not allowed. Snacks and beverages are permitted.

Inspectors must not conduct any type of inspection without the presence of the escort or the company representative(s).

Inspectors must abide by company instructions and procedures during inspection visit.

8. Mandate to inspect:

Based on the Public health law no. 20 the year 2004 and the pharmaceutical ordinance no. 19 the year 2006 of the PNA, the MOH is entrusted with the mission of enforcing Good Manufacturing Practice so as to protect consumer health. The Ministry is responsible for conducting comprehensive regulatory monitoring of all aspects of production and control of Pharmaceutical products

and APIs. Monitoring of such activities is intended to ensure that such products meet WHO GMP requirements to ensure their safety, quality and efficacy at all times through their life cycle.

This includes but is not limited to:

- Evaluating through factory inspections the conditions and practices under which pharmaceutical products and APIs are manufactured, packaged, tested and stored.
- The inspections may include the collection and analysis of associated samples as appropriate.
- Monitoring the quality of pharmaceutical products and APIs through surveillance activities such as sampling and analyzing products.

In order to ensure GMP enforcement, the Ministry of Health has set a target to inspect every company at least once a year for GMP and manufacturing license renewal. The time period between inspections shall not exceed two years.
The inspection frequency may be changed according to companies GMP compliance profile. The level of follow-up required is based on recognition of a company's documented compliance profile.
Organizing inspections is under the sole responsibility and authority of the Drug Control and Registration Department and they have the right to bring competent consultants for certain areas as needed. Inspections may be announced or unannounced depending on inspection types (see section 10).

9. Inspection Policy:

The general policy of inspection includes the commitment to assure compliance, quality of manufacturing and control process and quality of products.
Policy issues covers:

- Photographs: inspectors have the right to take photographs or short video shots for the specific area/equipment supposed to be not in-compliance in the presence of the company representative(s).
- Sampling: inspectors are allowed to take samples from any raw material, finished product, bulk and in-process material for analysis purposes only. They are not allowed to take samples for personal use.
- Complaint files: inspectors are allowed to review complaint and recall files.

- Internal Audits: inspectors are not allowed to review internal audits findings of the visited company; however they are allowed to assure that internal audits are conducted according to procedures and timetable as determined by the company.
- Copying Documents: inspectors may ask to copy documents and procedures for revision purposes only.
- The inspector has the legal right to enter licensed premises where any regulated activity is suspected to be carried out
- The inspector has the legal right to seize materials that are not in compliance with the regulatory requirements or represent a threat to public health
- The inspector has the right to require the company to suspend operations that are not in compliance with the regulatory requirements or represent a threat to public health

10. Types of GMP inspections:

The objectives of the inspections always influence the inspectors planning, organization, method of work and format of the resultant report that will be written after the inspection. Different types of inspections shall be performed depending on the objective of the inspection. These types as identified in WHO text include:

- **Comprehensive / Routine inspection**:

  This is a full inspection of all GMP components which may be conducted when the manufacturer:
  - Is newly established.
  - Request renewal of a license
  - Has introduced new products, or has made significant changes in key personnel, premises, equipment...etc.
  - Has a history of non-compliance with GMP.

  This type of inspection is going to be announced.

- **Concise inspection**:

  Known as an abbreviated inspection, which is normally conducted to evaluate limited aspects relating to GMP compliance within a facility, selected by the inspector to serve as indicator of overall GMP compliance by the manufacturer.

A concise inspection is applicable under the following circumstances:

- Consistence record of compliance with GMP.
- Identify significant changes.
- Indicates attitudes towards GMP.
- Where a sample of aspects can be taken as a good indication of the overall level of the GMP compliance.

However, if evidence of GMP performance observed during a concise inspection, a more comprehensive or full GMP inspection shall then be performed soon after the concise inspection.

Manufacturers will not normally be warned in advance about the concise inspection.

- **Follow-up inspection**:

Also referred to as a re-inspection or a re-assessment of the manufacturer. Follow-up visits are made to monitor the results of corrective actions. They are carried out from six weeks to six months after the initial inspection, depending on the nature of defects and the work required. They are limited to specific GMP requirements that have not been observed or that have been inadequately implemented.

This type is not usually announced.

- **Special inspection**:

There are many circumstances in which special visits or inspections may be undertaken. A special inspection is undertaken to do spot checks that focus on one product, a group of related products, or specific operations. It is applicable under the following circumstances:

- Following complaints or recalls.
- Reports of adverse drug reactions.
- Marketing approval or export certificate.
- To gather specific information on/or to investigate specific operations.
- To advise manufacturers on specific regulatory requirements.

The manufacturer normally will not be informed in advance of the inspection except in the cases of marketing approval.

11. Organizing Inspections:

11.1. Inspection Planning:

Authorized DDCR inspectors perform GMP compliance inspections and maintain monitoring records, which ensure that each company receives appropriate inspectional coverage. GMP compliance inspection will generally be conducted annually unless earlier inspection is warranted within this time period.

The first step is to define the objective of the inspection that is to be carried out, the type of inspection to be performed, the depth of the inspection, timing of the inspection and the inspectors who are going to conduct the inspection.

When the first step of inspection is decided the following, where applicable, will be notified:

- Inspection team members
- external consultant/ specialists

The manufacturer shall be informed of the inspection and the proposed times and the primary schedule at least ten days before starting the visit, if applicable. Other interested parties shall be informed of the proposed or planned inspection. This could include evaluators of the registration files, as they may request to investigate any aspect of the file or submitted data during inspection.

In preparing for the inspection, some documentation relating to the manufacturer shall be reviewed. These documents include site master file, manufacturing license, registration files, reports on previous inspections and adverse drug reactions, and records of the company in relation to complaints and recalls.

For pre-announced inspections, a production schedule may be requested, so that dates of the inspection can be coordinated. This will allow for observation of actual production, packaging and control activities.

When reviewing the manufacturers documentation a checklist or aide mémoire may be prepared of the points, to be verified during inspection. The inspection program shall also be developed and the manufacturer and the inspection team shall be informed of it.

11.2. The systems approach:

This guideline covers eleven key systems and three critical elements within each system for inspection.

The eleven key systems are:

1. Quality Assurance system.
2. Premises and equipment system.
3. Materials system.
4. Production system.
5. Packaging and labeling system.
6. Quality control system.
7. Research and development system (R & D).
8. Engineering and maintenance system.
9. Utilities system.
10. Warehousing and weighing systems.
11. Validation system

The three critical elements are:

1. Standard operating procedures (SOPs).
2. Training.
3. Documentation.

11.2.1. Quality Assurance System:

The quality Assurance system is meant to assure overall compliance with GMP, internal procedures and adherence to specifications. The system includes but not limited to all the reviews and approval of documents, release of components and in-process materials, change control, reprocessing, batch release, annual product review, validation protocols and reports, training, deviations and investigations, complaints and recalls, self inspection, audits to suppliers, all product defect evaluations and evaluation of returned and salvaged pharmaceutical products and batch production record evaluations (BPR).

Assessment of the quality system can be divided into two phases:

1. The first phase is to evaluate whether the QA unit has fulfilled its responsibility to review and approve all procedures related to production, quality control and quality assurance, and to ensure that procedures are adequate for their intended use. This also includes the associated record keeping systems.
2. The second phase is to assess the data collected in order to identify quality problems that may be linked to other systems.

11.2.2. Materials system:

This system includes measures and activities to control components containers and closures, printed packaging materials and finished products it includes purchasing controls, warehousing, separation of raw materials and finished products according to release status, validation of computerized inventory control processes, storage, distribution control and records.

11.2.3. Premises and equipments systems:

This system includes measures and activities that provide an appropriate physical environment, along with the equipment and resources that are used in production of pharmaceutical products. Coverage of this system includes verifying the appropriateness of building and facilities including maintenance; equipments qualifications (I.Q, O.Q, P.Q); equipment calibration /Validation and preventive maintenance; cleaning and validation of cleaning procedures as appropriate .Process performance should be evaluated as part of inspection of all overall process, which is done within the system where the process is employed:

11.2.4. Production system:

This system includes measures and activities to control the manufacture of pharmaceutical products including batch compounding, production and handling, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved

manufacturing procedures. Cleaning procedures and cleaning validation should be verified as part of this system.

11.2.5. Packaging and labeling system:

This system encompasses the measures and activities that control packaging and labeling of drugs and pharmaceutical products. Inspectional coverage should include review of the firm's written procedures regarding packaging and labeling controls. The firm's examination of labels and usage, label storage and issuance, packaging and labeling operations controls including line clearance, reconciliation, electronic means of inspection of printed packaging materials and validation of these operations should also be observed during inspection.

11.2.6. Laboratory control system:

This system includes all the various measures and activities that are related to laboratory procedures, analytical methods development, validation or verification, stability program and reserve samples. An in-depth audit of this system should include review of the firm's SOPs and methods for control of microbiological contamination and environmental monitoring, review of records for source of materials, in-process and finished product testing, evaluation of the methods for sampling and testing products for identity, potency, safety, sterility and conformance with final specifications, and review of the tests methods to ensure that they have been appropriately validated.

Organization and personnel, including verification of appropriate qualification and training will be evaluated as part of each system's operation.

11.2.7. Research and development system (R & D):

This system includes all the measures and activities that are related to new and old products formulation and control development. An in-depth audit of this system should include evaluation of development procedures, formulation facilities, raw materials and packaging materials specifications, stability studies of new formulations, scale up procedures, methods development and qualification, and prospective process validation.

11.2.8. Engineering and maintenance system:

The system encompasses all the measures and activities related to engineering and maintenance. Inspectional coverage should include:

- Training/qualification of personnel.
- Standard operating procedures and documentation.
- Calibration programs and records.
- Preventive and corrective maintenance schedule records for facilities and equipments.
- Purchasing specifications and receipt of new equipments.
- Equipment design and qualifications.
- Facility planning and drawings.
- Alarm systems and procedures.
- Filters integrity tests and records.
- Airflow and air changes tests and records.
- Lubricants approvals and receipts.
- Spare parts purchasing and storage.
- Maintenance of tablets punches and dies.

11.2.9. Utilities system:

The system includes all the activities concerning HVAC systems, pharmaceutical waters, steam, pharmaceutical gases and compressed air.

11.2.10. Warehousing and weighing systems:

These systems include all the various measures and aspects that are related to warehousing of raw materials, packaging materials, finished products, bulk products, flammable materials, rejected materials and products and recalled products.

11.2.11. Validation system:

The validation system includes the activities related to qualification and validation of facilities, utilities, materials, equipments, personnel, analytical methods, cleaning procedures and process validation.

12. Conducting inspection:

As previously discussed, there is a program for the inspection and this should include a draft timetable, while every visit will be different in the details, there will be some standard approaches:

- Opening meeting

  Attendees at this meeting should include the lead inspector and inspection team members and key quality and operational personnel from the site. The meeting should include an outline of the agenda and timetable for the inspection.

  Presentations can be made by the company at this time, outlining key changes at the facility since the last inspection.

- Plant Tour

  It is useful to have an orientation tour of the plant, particularly if it is the first time that the firm is visited. It should be emphasized that it is an initial walk-through only; detailed discussion must not be done at this point.

- Inspection

  The main activities of the inspection are to assess compliance with GMP. At some point in the inspection, it will be necessary to review the program and see whether it needs to be revised in the light of the information that has been obtained. The inspection then continues using the revised plan, taking into consideration that the persons involved in the inspection are aware of any changes, so that they can amend their plans accordingly. Inspectors should understand that employees at all levels of management feel under pressure during a regulatory inspection. It is important to be polite and to allow sufficient time for responses to be made. All questions should be answered, however there is always the possibility that a question has been misunderstood and therefore inspectors should be patient and willing to repeat and/or clarify a question until satisfied that an answer has been provided.

- Inspection findings

  There should be some time at the end of the visit, or as agreed upon with the escort, to review the findings. Any possible citations should be discussed and reviewed against the applicable WHO standards.

- Exit Meeting

  The last activity at the company is an exit meeting with the management team. The draft inspection report shall be discussed and issued to the company with citations and where applicable recommendations for actions.

- Taking samples:

It is a normal practice for the inspector to take samples during an inspection for testing purposes in the official quality control laboratories. Samples are usually taken from released products, from raw materials or in-process materials.

They must be collected by the inspector in the presence of the company's escort or representative, or if the company wants to sample the product or material, it should be done under the supervision of the inspector.

It is critical that the integrity of the samples is maintained. Therefore the inspector is required to check with the company regarding sample container and storage conditions and document these at the time of sample receipt.

Adequate quantities should be collected from the same batch(s) and divided into three equal portions:

- ❖ One portion should be kept in a sealed container which is signed by the inspector and the responsible person of the company and kept in the company to serve as reference in case of controversy.
- ❖ The second portion should be given to the company's "escort" for "in-house" testing.
- ❖ The third portion should be taken by the inspector for testing by the official quality control lab.

13. Classification of observations:

1. CRITICAL DEFICIENCY
A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2. MAJOR DEFICIENCY
A non-critical deficiency:
which has produced or may produce a product, which does not comply with its marketing authorisation;
or
which indicates a major deviation from WHO Good Manufacturing Practice;
or
(within WHO) which indicates a major deviation from the terms of the manufacturing authorisation;
or
which indicates a failure to carry out satisfactory procedures for release of batches or (within WHO) a failure of the authorised person to fulfil his/her required duties;
or
a combination of several “other” deficiencies, none of which on their own may be major, but which may together

3. OTHER DEFICIENCY
A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.
(A deficiency may be “other” either because it is judged as “minor” or because there is insufficient information to classify it as major or critical)

Examples of inspection findings are outlined in ***annex 1***. The list is not exclusive

14. Writing the inspection report:

Each inspection should be documented during the course of inspection in a bound notebook, wherever possible observations should be recorded immediately. Fast communication of findings is essential especially in cases where a real or potential danger to public health is discovered.

The inspection reports are primarily written in Arabic. If reports are required by other mutually recognized agencies they shall be translated by the Ministry of Health under the supervision of the Director of DDCR.

The Director of DDCR shall approve the translated report.

Each inspection team member writes the part he/she has inspected. The team leader has the over all responsibility for the final report. He/she must remove inconsistencies between the various parts and ensure that logical conclusions drawn are valid and factual.

The report is to be signed by all the team members and shall be approved by the DDCR. Director

The report should be submitted to the company within 30 days of the close-out meeting.

14.1. Report contents:

The inspection report should be prepared as a brief, factual statement of findings and should be specific and accurate. Inspection observations should be organized under section headings. Observations should be listed in order of importance within each system. Unsubstantiated conclusions should be avoided. Personal opinions without reference must be avoided. The report should reflect performance of a thorough, professional and efficient GMP inspection resulting in an impartial evaluation of the company's current state of compliance with GMP requirements. The report should be divided into four parts as follow:

Part 1: General information about the company; which can be taken directly from the information provided by the company.

Part 2: Description of the inspection, listing all parts of the factory, warehouse, laboratory …etc that have been inspected and all the obstacles faced during the inspection.

Part 3: Observations: either negative or positive, including any major changes (improvements and deterioration) that have been taken place since the previous visit. Positive observations should be a description of the process that is carried out particularly well. Negative observations should differentiate between poor systems and failure to comply with the system as defined in section 13.

Part 4: conclusion and recommendation: Consists of the inspector's summary and conclusion.

14.2. What should not be included in the report:

There are some aspects that should not be included in the report:

- Inspector's subjective opinion.
- Information that is not relevant to the inspection.
- Ambiguous statement that cannot be supported.
- Antagonistic statements that do not contribute to the inspection.

14.3. The covering letter of the report:

After the report has been authorized by the DDCR, it should be sent with a covering letter to the company management. If the report concludes that improvements and corrective actions need to be implemented, they shall be summarized in the letter. Time limits for carrying improvements and corrections and the consequences of not doing so, shall be pointed out in the letter. Inspection reports shall be treated as confidential documents and shall not be submitted to any parts except the inspected firm.

15. Regulatory Measures and Enforcement:

Where critical findings result from an inspection, management should be made aware of the severity of the observations at the exit meeting. If appropriate, actions that may be implemented in accordance with public health law no. 20 the year 2004 and the pharmaceutical ordinance no. 19 the year 2006 of the PNA. These actions may include

- Product(s) hold.
- Product(s) recall.
- Shut down of production line, or lines.
- Withholding approval of new products or renewal of registration of existing product.
- In the event of break down of several systems and in particular where there is evidence of lack of authority and/or professionalism in the quality system, the factory may be closed down through the District Medical Officer.
- Suspension of issuance or withdrawal of GMP certificate of compliance.

Any of the above actions many continue until verification of implementation of satisfactory corrected action.

It is recommended that the firm can discuss with the DDCR director some findings before deciding upon the corrective actions plan .

For deficiencies, firms are permitted 30 days to define the corrective actions plan. The company's response to the inspection report should point out actions that have been taken or will be taken with target dates for implementation and follow-up. Target dates must reflect a reasonable time frame. When company management is unwilling or unable to provide adequate corrective actions in a reasonable time frame, formal non-voluntary action will be considered, as appropriate for the situation encountered. Laboratory tests that support observations of inadequate GMP procedures are considered strong evidence for supporting regulatory actions.

Failure of a system is considered to have occurred where there is evidence to support significant and/or a trend of deficiencies within that system. The initial assessment and decision should be based on the seriousness and/or the frequency of the problem.

16. Follow-up:

Compliance inspections are performed to evaluate or verify implementation of corrective actions after enforcement action has been taken. The coverage given in compliance inspections should be related first to those areas found deficient and being corrected.

In addition a determination must be made on overall compliance status of the firm after the corrective actions are taken.

The firm is expected to address all of its operations in its corrective action plan not just the deficiencies noted in the audit report.

The full inspection option should be used for a compliance inspection especially if abbreviated option was used during the prior inspection.

References:

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Annex (1)

Examples of inspectional findings

Some examples of findings indicating lack of GMP compliance are provided below. These examples are not exclusive but are provided as guidance only.

Quality systems:

1. Failure to review / approve procedures.
2. Failure to record performance of operations as required.
3. Failure to review documentation, including annual product review, review of critical systems and review/approve change control procedure.
4. Failure to conduct investigations including OOS results and resolve discrepancies/failures/deviations/complaints.
5. Failure to assess other systems to assure compliance with GMP and SOPs, including failure to perform internal audits and vendor audits.

Facility systems:

1. Contamination with objectionable microorganisms, toxic chemicals or other drug chemicals.
2. A reasonable potential for contamination, such as air borne or through unclean equipment.
3. Lack of validation of HVAC and dust collection systems.
4. Lack of validation of water systems.
5. Failure to document investigation of discrepancies.
6. Failure in the design and construction of sterility test room to facilitate cleaning and disinfection.
7. The direction of air flow is not monitored in the manufacturing rooms.
8. There are no approved procedures for maintaining the HVAC and dust control systems throughout the plant.
9. There are no written procedures covering pest control within the buildings.
10. The design and construction of purified water treatment system revealed dead legs, which are potential sites for microorganisms to lodge, multiply.
11. There are no temperature or humidity specifications for the area.

12. Sensors for monitoring have not been calibrated since their installation.
13. Circulated air has never been tested for particulate matter.

Equipment systems:

1. Failure to document and investigate discrepancies.
2. Failure to follow a change control system for equipment.
3. Equipment systems were not adequately qualified (IQ, OQ, PQ).
4. Worst-case conditions are not undertaken during the validation study.
5. Cleaning failures noted in the ongoing cleaning validation program are not investigated and corrected.
6. The maintenance person was using an obsolete SOP for maintenance and calibration of equipment.
7. The firms cleaning validation program has not addressed how long a product can remain in the processing equipment before the equipment must be cleaned.
8. There are no maintenance records for the machines to indicate when routine repairs and replacement of parts is performed.
9. Filters used to sterilize bulk drug solutions are not being subjected to a prefiltration integrity test.
10. There are no written procedures for calibration and preventive maintenance of laboratory instruments.
11. Lack of adequate recording systems for calibration of sensors.

Materials system:

1. Some materials (i.e. ……) are released for use and distribution which do not conform to established specifications.
2. Failure to conduct identity test for components.
3. Failure to document investigation of discrepancies.
4. Lack of auditing vendors.
5. There were no vendor responses to audit reports and observations.
6. Sampling procedures and plans of containers/closures is not based on appropriate statistical criteria.
7. The firm has not included a pyrogen and/or bacterial endotoxin specification for active drug substance raw material.

8. No explanation was given in the process validation report as to how bulk density affects the finished product.
9. Several batches were rejected because the active raw material did not meet the firms established bulk density specifications.
10. The firm is aware that (certain product) has shown marked degradation over time but no testing was performed on current lots in order to justify the material storage time limitation.
11. No procedure available describing the FIFO principle of dispensing and distribution.
12. Products requiring specific storage conditions 15°C – 30°C were stored in a non air conditioned store at more than 32°C.
13. No defined quarantine area for incoming materials.
14. No defined quarantine area for incoming finished products to be packed/repacked.

Production and process control system:

1. Failure to follow a control system for implementing changes in the production system operations.
2. Failure to document investigation of discrepancies.
3. Lack of process validation.
4. Lack of validation of computerized systems.
5. Incomplete or missing batch records.
6. Nonconformance to established in-process controls, tests, and or specifications.
7. Revalidation of the sterility test room was not performed as required by the firm's procedures.
8. The master formula and procedures do not state a time limit for holding filtered solutions prior to filling and terminal sterilization.
9. Batch manufacturing instructions do not provide sufficient written detail to ensure the uniformity of the production process from batch to batch.
10. There is no final summary to verify that the validation data has been reviewed, that all requirements of the protocols have been met, and the systems are considered validated.
11. The validation program for drug products is incomplete and fails to provide for physical specifications for drug substances.

12. The SOP for validation or revalidation does not require that specifications and acceptance criteria be determined prior to validation.
13. There were no SOPs for the QA investigations for product failures.
14. Validation of tablet products is inadequate in that it does not include tablet thickness, hardness, weight, or dimensions.

Packaging and labeling:

1. Failure to follow a control system for implementing changes in packaging and/or labeling operations.
2. Failure to document investigations of discrepancies.
3. Lack of validation of computerized systems.
4. Lack of control of packaging and labeling operations that may introduce a potential for mislabeling.
5. Lack of packaging processes validation.
6. The firm uses cut labels. There is no record 100% visual inspection that was repeatedly performed.
7. There are no procedures for evaluation of discrepancies found between the quantity of finished drug product and the quantity of labeling issued.

Laboratory control system:

1. Failure to follow control system for implementing changes in laboratory operations.
2. Failure to investigate discrepancies.
3. Lack of validation of computerized/automated data collection systems.
4. Inadequate sampling procedures/practices.
5. Lack of documentation in laboratory notebooks.
6. Standards not adequately maintained and calibrated.
7. Laboratory instrumentation inadequately maintained/calibrated/qualified.
8. Lack of validated analytical methods.
9. Failure to follow approved analytical procedures.
10. Failure to follow an adequate OOS procedure.
11. Failure to retain raw data.
12. Lack of stability indicating methods.
13. Failure to follow stability programs.

14. SOPs uses statistical outlier test to invalidate OOS results, statistical outlier tests are inappropriate for use with validation methods.
15. Data acceptance/rejection was done selectively.
16. Stability testing SOPs contained no provision for increased testing of either additional lots or additional intervals or shortened intervals after confirmed failures.
17. There are no data to show that the methods used to analyze stability samples were validated as stability indicating with respect to acid and base hydrolysis, oxidation, thermal degradation and pyrolysis.
18. The firm used the service of an outside microbiology laboratory. The laboratory had never been audited by the firm.
19. Chromatograms are run for long time without additional solution injections to check on the stability of the chromatographic system.
20. There are no criteria established for OOS results defining at what points testing ends, products are evaluated, and rejected if results are not satisfactory.
21. Stability test failures are not reported to the regulatory department in MOH.

Organization and personnel:

1. There was an insufficient personnel for performance of the quality control activities.
2. The GMP training program is inadequate in that it does not define the level, type, and schedule of GMP training required for various employee positions.

Records and reports:

1. Theoretical yields and actual yields are not determined for every batch.
2. The firm's written procedures for the investigation of complaints is inadequate.
3. Complaint investigation does not include written justification for why investigation did not extend to other batches.
4. The annual product review for (certain product) is inadequate in that it only consists of a table listing lots manufactured during the year and content uniformity values for ten capsules in each lot. No additional information is contained in the report.

5. Retain samples. A number of products (name them) were found not to have been reviewed according to the annual product review programme. There was no follow-up to any of these product deficiencies. There are no retain samples for ……. Batches manufactured during the year.

Returned and salvaged products:

1. Reason for product return is not documented.
2. No evaluation of the cause of the returned product.
3. No validation of reprocessing of tablets from compression machine set up