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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Macleods Pharmaceuticals Ltd
Physical address – production departments	Macleods Pharmaceuticals Ltd, Unit 2, Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, 396 210, India
Unit	Unit II
Phase	Phase I
Postal address	As above
Dosage form included in the inspection	Sterile powder for injection
WHO product numbers covered by the inspection	• TB211 Capreomycin (sulfate) Powder for solution for injection 1000mg • TB212 Kanamycin (as acidsulfate) Powder for solution for injection 500mg • TB213 Kanamycin (as acidsulfate) Powder for solution for injection 1000mg • TB214 Streptomycin (sulfate) Powder for solution for injection 1000mg
Type of inspection	Routine inspection
Date of inspection	18 – 22 April 2016
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control, stability testing, storage and distribution of: • Powder for solution for injection • Tablet – coated and uncoated

Part 2: Summary

General information about the company and site

Macleods Pharmaceuticals Ltd (further referred to as Macleods) has the following manufacturing sites:

Formulations

- Plot No 25-27, Premiere Industrial Estate, Kachigam, Daman (U.T.)
- Plot No.7-9, Ganesh Industrial Estate, Daman (U.T.)
- Plot No 367/7, Kabra Industrial Estate, Daman (U.T.)
- Plot No 1, Mahim Road, Palghar, Maharashtra
- Theda Village, Nalagarh, Himachal Pradesh
- Plot 21 Aho Yangtam, Namchepung Ranipool, East Sikkim, Sikkim

and API manufacturing site at: Plot No 2209, GIDC, Sarigam, Gujrat.

The following product range was manufactured by the Macleods:

- Anti-Tuberculosis
- Anti-Malarials
- Anti-Retrovirals
- Anti-Bacterials
- Proton pump inhibitors
- Cardiovasculars
- CNS agents

Inspected site had three production blocs (phases) – FPP (two) and injectable manufacturing block.

History of WHO or regulatory agencies inspections

The Phase I was last inspected by WHO in June 2012. The site has also been inspected by the following regulatory authorities:

- MOH – Ukraine
- TFDA – Tanzania
- NDA – Uganda
- MCAZ – Zimbabwe
- MOH – Namibia
- MCC – South Africa
- PPB – Kenya
- FDB – Ghana
- MOH – Ethiopia
- IDA – Netherlands

Focus of the inspection

The inspection covered sections of the WHO GMP for sterile products text, including quality assurance, premises, equipment, documentation, validation, production and manufacture related to the products listed above.

Inspected Areas

- Quality Assurance
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Vendors evaluation
- Contracts
- Premises
- Equipment
- Documentation
- Production
- Quality control

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Principle

In general PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release and regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

Quality Risk Management (QRM)

The SOP "Quality risk management" was discussed. The SOP was applicable for risk management for all processes/systems and Corrective actions and preventive actions. Risk analysis was used for:

- Validations and all levels
- Change control/deviation execution
- Incident reporting and investigation
- Investigation for any failure/non-conformance
- Handling market complaints
- Development of product specification and critical process parameters
- Out of specifications (OOS)/ out of trends (OOT)/out of calibration investigations

Two tools were used for RA:

- Failure mode effect analysts (FMEA) – mainly was applied for equipment's; scoring from 1 to 10 was used to define RPN
- Hazard analysis and control points (HACCP) – product RA

RA protocol numbering log for 2015, 2016 and annual risk review year 2015 were presented to the inspectors.

The “Risk analysis protocol for AHUs system in injection area (dry powder injection)” XX was discussed.

The “Risk analysis protocol for steam sterilizer Cum Bung processor (autoclave)” YY was discussed.

The “Risk analysis protocol for risk associated with modification of phase I injection area” ZZ was discussed.

Product Quality Review (PQR)

The SOP “Product quality review” was discussed. PQE were done annually starting from the date of manufacturing of the first batch in a year. According to the SOP, PQR schedule should be prepared every month. PQR data were presented as tabulated and graphs. According to the SOP review should be done if ten or more batches were manufactured. In cases less than ten batches were manufactured, PQR shell be prepared considering date from cumulative batches of previous years.

The PQR for Streptomycin for injection BP 1g (January 2015 to December 2015) was discussed.

Deviations

The SOP “Handling of deviation” was discussed. Deviations were classified as:

- Unplanned
- Planned

According to the SOP formal risk analysis (RA) should be done for each deviation. Based on RPN numbers calculations and risk should be categorized as low/medium/high. For medium and high risk, full scale RA should be performed as per RA SOP. Based on the nature of deviation (critical, major and minor) corrective and preventive actions (CAPA) should be proposed. Timeline for closing the deviations was specified 30 days.

Change control (CC)

The SOP “Change control” was discussed. The SOP was applicable for:

- SOPs, specifications and other documents
- Batch manufacturing records (BMR)/batch packaging records (BPR)
- Formats
- Validation
- Vendors
- New product manufacturing
- Facilities
- Equipment/instruments

Changes were classified as:
- Minor
- Moderate
- Major

Corrective actions and preventive actions (CAPA)
The SOP "Corrective action and preventive action" and register were discussed. Tools used for root cause investigation was specified:
- Ishikawa diagram
- 5 Why analysis

The SOP was applicable to:
- Deviations
- Out of specifications
- Non-conformances
- Product recall
- PQR
- Returned goods
- Market complaint
- Quality risk assessment
- Self-inspection
- Validation/qualifications
- Out of Trend
- Heavy rejections
- Failure investigation
- Any regulatory / customer requirement

CAPA XX and related OOS investigation form YY were discussed

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Manufacturing processes were clearly defined and systematically reviewed. Qualifications and validations were performed. Necessary resources were provided and records were made during manufacture. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. A system was available to recall any batch of product from sale or supply and complaints about marketed products were examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products.

3.3 SANITATION AND HYGIENE

The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facilities. Areas were cleaned frequently in

accordance with an approved written program and SOPs. Microbial monitoring was regularly performed.

3.4 QUALIFICATION AND VALIDATION

Validation Master Plan (VMP)

The key elements of a qualification and validation program were defined and documented in the validation policy. Phase I validation master plan (VMP) was presented to the inspector. Separate VMP was available for Phase II.

Qualification

Requalification protocol No XX for sterilizing and dehydrogenation tunnel was discussed. Requalification was performed every 6 months.

Aseptic process validation

The SOP "Aseptic process simulation" and certificate of analysis (CoA) Soybean Casein Digest Medium sterile powder (lot No XX) were discussed.

Aseptic process validation was carried out twice per year ± 1 month. Vials were filled with sterile SCDA media, supplemented with WFI. 10 000 vials were filled and 1 run was carried out for each vial size. Interventions were included in the media fill. Weight and volume checks of were carried out. For process simulation minimum, optimal and maximum filling speed was used. According to the SOP medial filling activity shall be performed to cover two operation shifts, duration of the run shall adequately mimic worst case operation conditions and cover all interventions that are performed in the actual processing operation.

Media fill XX ml vials batch manufacturing record No YY was discussed. Vials were inspected by the visual inspectors and microbiologists. Vials were inspected:

- Before incubation
- After one day incubation
- After 7 days incubation
- After 14 days incubation

The SOP "Media fill failure investigation" was discussed.

Autoclave validation

The Steam sterilizer cum bung processor re-qualification protocol/report XX was discussed. A number of sensors were used for heat penetration during the re-qualification -stationary condition. A number of biological indicators were used for rotation position re-qualifications. After re-qualification rubber stoppers sterility test, particle count tests, bacterial endotoxin test and rubber stopper moisture test were carried out. Bacterial endotoxin test were carried out also for condensate sample.

3.5 COMPLAINTS

The SOP "Handling of customer complaint" was discussed. The SOP was applicable for product complaints. Head QA was responsible for handling of complaint. Complaint was categorized as:

- Critical
- Major
- Minor

Complaints were trended quarterly, half yearly and annually.

A specific complaint investigation was discussed.

Complaints trends for 2015 were discussed.

3.6 PRODUCT RECALLS

The SOP "product recall" was discussed. Head site QA and plant manager were responsible for monitoring and coordinating activities related to product recall. Two types of recall were specified:

- Voluntary recall
- Forced recall

Recalls were classified as:

- Class I – action was required within 24 hours
- Class II – action was required within 48 hours
- Class III – action was required within 5 working days

Effectiveness of the procedures was evaluated by the mock recall (separate for domestic and export markets), what should be performed every two to three years ± 3 months. Last mock recall was executed on 26/08/2014 for export market.

3.7 CONTRACT PRODUCTION AND ANALYSIS

Manufacturing operations were not contracted out. Some laboratory tests (pyrogenity and toxicity) were contracted out.

3.8 SELF INSPECTION, QUALITY AUDITS AND SUPPLIERS AUDITS AND APPROVAL

The SOP "Procedure for self-inspection" was discussed". Self-inspection schedule January 2016 – June 2016 was presented to the inspectors. Spot checks showed that the schedule was followed.

Items for self-inspection

The following areas were covered by the self-inspection:

- Organization and personnel
- Buildings and facilities
- Equipment
- Control components and drug product containers and closures
- Production and process control
- Packaging and labeling control
- Holding and distribution
- Laboratory controls
- Records and reports for appropriateness of data and data integrity
- Returned and salvaged drug products

Self-inspection team

List of the self-inspection team members was presented to the inspectors.

Frequency of self-inspection

According to the SOP each department should be inspected once in six months.

Self-inspection report

Self-inspection was carried out according to the department visewise check-list. After inspection self-inspection report was written and signed by the team members and approved by the QA manager/designee.

Follow-up action

CAPAs were submitted by the inspected department head, reviewed by the team and approved by the QA manager/designee. If required follow-up self-inspection was carried out.

Supplier's audits and approval

The SOP "Vendor Qualification and approval" was discussed. Commitment shall be obtained from all authorized supplier/agent that they are not permitted to do repackaging; relabeling and they will provide the CoA supplied by the authorized manufacturer, confirmation of storage conditions, whenever applicable".

3.9 PERSONNEL

General

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

List of the persons who were allowed to enter the aseptic for media fill participation area was presented to the inspectors. Access to the core areas was biometric.

The SOP "Operation of biometric system" was discussed. The SOP defined six different access levels.

Job descriptions (JD)

Job descriptions were available for all personnel.
Organogram for production and Quality control were presented to the inspectors.

The following JDs were disused:

- Assistant general manager (responsible for product release), authorized deputies were specified in JD.
- Manager II, Quality Assurance
- Deputy manager, Quality Assurance

Training

The SOP "Training of personnel" was discussed. According to the SOP there were the following types of training:

- Induction training
- On-job training
- Annual training
- Advanced training

Training effectiveness was evaluated by written questions (true/false) or orally. Refreshing training was carried out annually. Training skill matrixes (groups) were discussed. Monthly training schedule was presented.

GMP - training module XX was discussed. Some parts of module was in English and local language, some only in English language. Training module contained the following parts:

- Preparation of cleaning and sanitization solution in manufacturing
- Do`s and don`ts in production areas
- Good manufacturing practices
- Good laboratory practices
- Safety
- Documentation
- Aseptic areas practices

The training module YY "Sterile pharmaceutical products" was discussed.

Personnel hygiene

The SOP "Procedure for personnel hygiene" was discussed. Personnel suffering from illness such as skin rashes, colds, and open lesions to the body were required to report the department head and were excluded from working in the clean and critical areas. Smoking,

eating, drinking, chewing and the storage of food and personal medicines and smoking was prohibited in the manufacturing areas.

The SOP "Procedure for medical check-up" was discussed. This SOP was applicable to the permanent workers. It was noted that contract workers were involved in secondary packaging of the products. According to the SOP all personnel should undergo medical examination prior to recruitment and annually, eye testing (sight/vision testing) for optical/visual inspectors shall be performed on half year basis.

3.10 PREMISES

General

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Airlock doors were interlocked.

Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas

Storage areas were of sufficient capacity. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products

Production areas

The production of sterile preparations was carried out in clean areas, entries to which were through airlocks for personnel and for equipment and materials. Clean areas were maintained to an appropriate standard of cleanliness and supplied with air that has passed through HEPA.

Quality control areas

Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

3.11 EQUIPMENT

General

Equipment was located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt.

Schematic drawing of the sterilisation tunnel and air flow patterns in tunnel were discussed. Tunnel had:

- Drying zone
- Hot zone
- Cooling/stabilizing zone

Tunnel was on higher pressure than surrounding area.

Preventive maintenance (PM)
The SOP "Preventive maintenance of sterilizing dehydrogenationdepyrogenation tunnel" was discussed. According to the SOP PM should be carried out every 3 and 6 months according to the check list. Annual PM schedule was presented to the inspectors, spot checks showed that PM schedule was followed.

3.12 MATERIALS

General
Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution.

Starting materials
Starting materials were purchased from approved suppliers. Approved suppliers lists for active pharmaceutical ingredients and packaging materials were available and presented to the inspectors. Sterile raw materials were stored in mobile racks.

Rejected materials
Rejected materials were stored in separate locked area.

Returned materials
The SOP "Handling od of market returned finished goods" was discussed.

Packaging material
For sampling, AQL testing procedure according to the ISO 2859-1 was used. Packaging materials defects were defined as:

- Critical
- Major
- Minor

Reference standards (RS) and working standards (WS)
RS and WS were stored in fridge and deep freezer and in room temperature (T). T in fridge and deep freezer was continuously recorded (interval 1 hour) and printouts were taken and checked daily. Fridge and deep freezer were equipped with alarm system.

WS were qualified against the RS and dispensed in amber vials for individual used. Traceability/reconciliation of the RS`s/WS`s were ensured.

3.13 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

Specifications and testing procedures

Standard test procedure "Finished product standard test procedure Kapocin 0.75 g (Capromycin injections)" was discussed.

Standard operating procedures (SOP) and records

Generally various SOPs and records of actions taken were available for all activities carried out on site. Records were kept for major and critical equipment.

3.14 GOOD PRACTICES IN PRODUCTION

General

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Access to production premises was restricted to authorized personnel. In-process controls were performed by operators.

Processing operations

Before processing operations was started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Necessary in-process controls and environmental controls were carried out and recorded.

Packaging operations

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously.

3.15 GOOD PRACTICES IN QUALITY CONTROL

General

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are carried out. QC personnel had access to production areas for sampling and investigation as appropriate.

HPLCs and GCs were connected to the Chromeleon 6.8 version software. UVs and IR were connected to the Class Agent (LC solution) software.

The SOP "User management for Chromeleon chromatographic data management system" was discussed.

Manual integration was explained in the SOP "Good chromatography practices".

In-process control (IPC)
IPC sampling – weights checks were done by operators.
Batch record review/batch release procedure
The SOP "Release of finished product batch" was discussed. According to the SOP executive/assistant Manager QA was responsible for reviewing the batch record, Head QA for release of batch. Batch audit check lists were used for product release.

The SOP "Review and approval of matchbatch manufacturing/packaging record". According to the SOP QA officer/executive/ assistant Manager/ deputy manager were responsible for reviving manufacturing/packaging record, Head QA for approval and release of batch. Batch review sheets were used for product release.

Analytical records review/ Certificate of analysis (CoA)
The SOP "Analytical raw data entry, verification and generation of certificate of analysis was discussed. According to the SOP QA officer/executive/Section head – QC and QA were responsible to review analytical data; Head of department QC was responsible for approving CoA. Check lists of analytical raw data and CoA was used for review of analytical data and CoA. During the review chromatograms print outs, method file prints and audit trial history, system suitability and etc. were reviewed and checked.

Out of specification results (OOS)
The SOP "Handling of out of specification results (chemical and physico –Chemical tests) and the SOP "Investigation of out of specification of tests results in microbiology", related flow carts and OOS investigation log books were discussed.

Microbiological laboratory (MB)
Environmental monitoring (EM) trends for grade A/B (January, February and March 2016) were discussed. For grade A there were no growth reported. Action and Alert limits were based on historical trend data.

The SOP "Procedure for environmental monitoring of injection area" was discussed. According to the SOP EM results were recorded per individual plate per 4 hours.

The SOP "Personnel monitoring in aseptic area" was discussed. The SOP specified sampling locations for gowns and finger dabs.

The SOP "Disposal of microbial cultures & culture media and cleaning of glassware/accessories used for microbial operations" was discussed. Destruction of media was carried out in separate autoclave.

Part 4: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report Macleods Pharmaceuticals Ltd, Unit 2, located at Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, 396 210, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.