

WHO PUBLIC INSPECTION REPORT (WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Macleods Pharmaceuticals Limited
Unit	Unit 2, Phase I
Physical address	Macleods Pharmaceuticals Limited Plot No. 25-27, Survey No. 366 Premier Industrial Estate Kachigam, Daman (U.T.) India
Contact address	As above
Date of Inspection	4 - 7 June 2012
Type of inspection	Routine inspection, covering selected aspects of GMP for sterile products
Dosage forms(s) included in the inspection	Powder for injection
WHO product categories covered by the inspection	Products under assessment Sterile Dry Powder Injections
Summary of activities of manufacturer (e.g. manufacturing, packing)	Manufacturing, quality control and batch release of sterile powders for injection and FPP: oral solid dosage forms (tablets - coated and uncoated) Cephalosporin's and Beta lactam Antibiotic products were not manufactured

Part 2: Summary

Background information

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

Formulations

- Plot No. 23-28, Premiere Industrial Estate, Kachigam, Daman (U.T.)
- Plot No. 8, 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

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

The total number of employees engaged on the site for Production, Engineering, Production Planning and Control (PPC), QC/QA, Stores and Distribution was about 188 employees. In addition, contract employees were involved in the secondary packaging operations.

History of WHO or regulatory agencies inspections

The Daman site was inspected by:

Sr. No.	Injectable	Tablet
1	WHO – (2004, 2005, 2007, 2010, 2011)	---
2	INVIMA – Colombia	---
3	SSMMD – Ukraine	SSMMD – Ukraine
4	NAFDAC – Nigeria	---
5	PMPB – Malawi	PMPB – Malawi
6	MCAZ – Zimbabwe	----
7	PPB – Kenya	PPB – Kenya
8	TFDA – Tanzania	TFDA – Tanzania
9	NDA – Uganda	NDA – Uganda
10	FDB – Ghana	FDB – Ghana
11	MOH – Namibia	MOH – Namibia
12	MOH – Botswana	MOH – Botswana
13	MOH – Ivory Coast	MOH – Ivory Coast
14	MOH – Yemen	MOH – Yemen
15	MOH – Ethiopia	MOH – Ethiopia
16	MOH – Belarus	MOH – Belarus
17	IDA – Netherlands	---
18	Mission Pharma – Denmark	---

The last routine WHO inspection at Daman site for sterile products was carried out from 30 May to 3 June 2011.

Focus of the inspection

The inspection focused on the production and control of the following products:

- Capreomycin 1g;
- Kanamycin Acid Sulfate 500 mg;
- Kanamycin Acid Sulfate 1 g;
- Streptomycin Sulfate 1 g.

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

Inspected Areas

- Quality Assurance.
- Qualification and validation.
- Complaints.
- Premises.
- Equipment.
- Documentation.
- Production.

2.1 QUALITY ASSURANCE

In general a system for quality assurance was established.

Quality Risk Management (QRM)

The SOP “Quality Risk Management” and Risk management manual was reviewed.

Tolls specified in the manual for Risk management were the following:

- HACCP;
- HAZOP;
- PHA;
- risk ranking and filtering;
- supporting statistical tools.

Risk analysis study (HACCP) for Product Capreomycin for BP 1,000 mg and Risk assessment study for Product Chloramphenicol Sodium Succinate injection BP 1mg were reviewed.

The following Risk index scoring was applied for risk assessment.

Risk Index	Score		
	1	5	10
Detectability	Easy	Moderate	Impossible
Occurrence	Improbable	Likely	Frequent
Severity	Low	Moderate	High

Product Quality Review (PQR)

The SOP “Product Quality review” (PQR) and PQR Capreomycin for injections 1000 mg PQR were reviewed.

Change control

The SOP “change control” and change control logs for 2011 and 2012 were reviewed. Changes were classified as:

- minor change;
- moderate change;
- major change.

Deviation management

The SOP “Handling of deviation” and relevant deviation forms were reviewed.

Corrective Action and Preventive Actions (CAPAs)

The SOP “corrective action & preventive action” and CAPA register were reviewed. The SOP was linked to deviations, non-conformances and market complaints.

CAPA assessment plan included but not limited to the following criteria:

- applicable regulations and guidelines to be followed;
- a review of internal Essential Regulatory Documents;
- facility inspections;
- monitoring self-inspection reports;
- pending or completed external audits;
- received complaints including concerns detailed in monitoring reports.

CAPA Program Flow chart was applicable for:

- audits/self-inspection;
- deviations/observations;
- OOC.

Tool used for CAPA investigation was specified:

- 6-M framework using Ishikawa diagram.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. The necessary resources were provided. Manufacturing processes were defined and reviewed. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. Environmental monitoring was regularly undertaken.

2.4 QUALIFICATION AND VALIDATION

Aseptic process validation

Media fill validation protocol and report and batch manufacturing record were checked.

Aseptic process validation was carried out twice per year. Vials were filled with sterile SCDA media, supplemented with WFI. 10,000 vials were filled and three consecutive runs were carried out for each vial size. Interventions were included in the media fill.

Autoclave validation

Autoclave IQ, OQ and PQ was carried out in February 2012 (for a new autoclave). In general, requalification was carried out twice per year for all loads. Last requalification was done in March 2012.

There were seven autoclaving loads validated. Re-qualification was done for the minimum and maximum loads (in triplicate). Autoclave capacity was 1010 L. 16 RTD sensors were used in heat distribution and heat penetration studies.

The following pure steam condensate tests were carried out:

- non condensable gases;
- degree of super heat test;
- dryness fraction test.

Microbiology autoclave validation

IQ, OQ and PQ protocols/reports were reviewed.

Sterilizing and dehydrogenization tunnel re-validation

Re-validation protocol and report were reviewed.

Re-validation was carried out using 7.5 ml and 20 ml vials and three runs for all cycles. Bacterial endotoxin challenge test was carried out. Re-qualification was carried out before media fills: February-March 2012.

Heat penetration and heat distribution studies, including the following tests were carried out:

- air velocity: it was noted and discussed with the company that FPM and not international standard (meter/second) was used for calculations in
 - dry zone;
 - hot zones;
 - cool zone.
- pressure differentials across the HEPA filters;
- DOP;
- non viable air born particle counts;
- viable particle counts;
- air flow pattern test.

Vials were tested for sterility and endotoxin (LAL test).

Cleaning validation

Cleaning validation was briefly discussed. Cleaning validation was based on “worst case product” approach. Validation studies were carried out using swab samples and rinse samples.

AHU qualification

AHU No. 23 serving injection department qualification and re-qualification protocols/ reports were spot checked.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written procedure.

2.6 PRODUCT RECALLS

Not inspected.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Not inspected.

2.8 SELF INSPECTION AND QUALITY AUDIT

Not inspected.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Contract workers were involved in the secondary packaging operations.

2.10. TRAINING

Not inspected.

2.10 PERSONAL HYGIENE

Not inspected.

2.11 PREMISES

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.

Grade A/B areas were not designed so that all operations can be observed from outside. However video cameras were installed in filling and crimping room, so aseptic filling and crimping could be observed on several TV screens.

Quality control areas

Not inspected.

2.12 EQUIPMENT

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.

2.13 MATERIALS

Culture media

Records for the receipt and preparation of culture media were available. The company followed media manufacturers instruction for media sterilization. Growth promotion tests were carried out as well as positive and negative controls.

2.14 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.

Batch Manufacturing Record (BMR) and Batch Packing record (BPR) for Hydrocortizone Sodium Succinate sterile powder for Injection 100 mg, were reviewed.

2.15 GOOD PRACTICES IN PRODUCTION

The production area was briefly inspected. This included the movement of materials, de-boxing of vials, washing and sterilization of vials as well as filling, stoppering and capping. Operations were observed (by camera and through the corridor). The particle monitoring during set up and continuous monitoring during filling was verified.

2.16 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. QC personnel had access to production areas for sampling and investigation.

Sampling

The SOP “Sampling, testing, release, reject of packing materials” was reviewed. Acceptance Quality Level (AQL) was applied for the sampling of packaging materials.

Packaging materials defects were defined as:

- critical;
- major;
- minor.

Handling of OOS results

The SOP “out-of-specification result investigation” and a number of OOS investigation reports were reviewed.

Microbiological laboratory

Two autoclaves were installed in the Microbiology laboratory, one for sterilization of media and one for destruction of biological waste material.

The company installed a new sterilization autoclave (capacity 113L) in February 2012.

Part 3: 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 Limited Unit 2, Phase I, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman (U.T.), India, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines for sterile 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 two years, provided that the outcome of any inspection conducted during this period is positive.