



WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Macleods Pharmaceuticals Ltd
Unit number	Unit VI (Baddi)
Production Block	N2
Physical address	Village Theda, P.O. Lodhi Majra, Tehsil Baddi, District: Solan, Himachal Pradesh 174 101, India
Contact address	Mr. Sushil Jaiswal sushil@macleodspharma.com
Date of inspection	14-17 July 2014
Type of inspection	Routine inspection, covering all aspects of GMP
Dosage forms(s) included in the inspection	Tablets, hard gelatin capsules and liquid oral dosage forms and pellets.
WHO product categories covered by the inspection	TB, HA
Summary of the activities performed by the manufacturer	Manufacturing, quality control and batch release of FPP: solid and liquid oral dosage forms

Part 2: Summary

General information about the company and site

Macleods Pharmaceuticals Ltd (referred to as “Macleods” in the rest of this text) had been manufacturing pharmaceuticals since 1986 and had five finished product manufacturing facilities in India, as well as one facility for active pharmaceutical ingredients. It was supported by its R&D and in-house bioequivalence centers in Mumbai. Sites participating in WHO Prequalification included:

- Daman - Solid oral dosage forms and Injectables (Dry Powder Injections)
- Baddi, Himachal Pradesh - Solid and Liquid oral dosage forms
- Sarigam, Gujarat - API manufacturing facility
- R&D and Clinical bioequivalence center, Mumbai.

The company, in total, had approximately 10,000 employees. The Baddi site was started in 2007. The site has three independent manufacturing facilities designated as Block N1 (Small tablet and soft gelatin block), Block N2 (General block), Block N3 (Cephalosporin block). Only Block N2 was being used for the above-listed WHO products. Only Block N2 was covered by this inspection.

The site held a valid license with the Food & Drug Administration of Himachal Pradesh.

History of WHO and/or regulatory agency inspections

The Baddi site has been inspected previously by several regulatory authorities, including the US FDA and UK MHRA.

The last routine WHO inspections of Macleods Baddi were carried out in February 2012 and in March 2009. In January 2011, the WHO inspection team carried out a biowaiver inspection.

Other Macleods sites, at the location of Sarigam and Daman, were recently inspected (May 2014).

Focus of the inspection

The inspection focused on the production and control of prequalified solid oral dosage forms products. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities

Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene

- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

Quality risk management (QRM)

The QRM SOP was reviewed along with randomly selected examples.

Product quality review (PQR)

PQRs were reviewed for a number of products, from January 2013 to December 2013. This area was generally considered to be satisfactory.

Deviation management

Trend analysis was performed once per year. The deviation register was reviewed and was found to be satisfactory.

Handling of non-conformances

A number of out-of-specification test results and associated investigation reports were reviewed. These were considered satisfactory in general, apart from a few minor issues which were resolved in the company CAPAs.

Corrective and Preventive Actions (CAPAs)

The procedure for corrective and preventive actions, dated July 2014, was reviewed. It applied to audits, deviations, incidents, out-of-specifications, out-of-trends, non-conformances, market complaints and recalls.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were adequately implemented, in general. The necessary resources were provided. Manufacturing processes were defined and reviewed. Qualification and validation was 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.

2.4 QUALIFICATION AND VALIDATION

The company identified the required qualification and validation work to be done for the year. The addendum to the equipment validation master plan was reviewed. The

key elements of the qualification and validation programme were defined in the validation master plan (VMP).

2.5 COMPLAINTS

The market complaints from 2014 were recorded in a register for all products. The procedure for complaints was reviewed along with its associated registers. Examples were randomly picked and recent WHO complaints were followed up. Root-cause investigation and CAPA were generally considered acceptable.

2.6 PRODUCT RECALLS

No recalls had been conducted since the last WHO inspection.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Finished product production operations and QC tests were not contracted-out.

2.8 SELF INSPECTION AND QUALITY AUDIT

Vendor qualification and approval was verified. The list of approved vendors was examined using the approved vendor list and PQRs in conjunction with the material management system for key WHO products.

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 but were under adequate strengthened supervision further to a complaint. Access control was used to prevent unauthorized people from entering production, storage and QC areas.

2.10 TRAINING

Training records were maintained for all permanent staff and on paper for contractual staff. The same modules were given at the time of induction and for scheduled training (established as per a calendar). Unscheduled trainings were performed when a new/ revised SOP was set in place. The training done on a new SOP for complaints that was implemented on 12/07/2014 was reviewed. The training was performed 11/07/2014 and a questionnaire was given to assess training effectiveness.

2.11 PERSONAL HYGIENE

Changing and washing was done following a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines were not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and

jewellery were not allowed in clean areas. This area was considered acceptable overall.

2.12 PREMISES

Production areas

In general exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning agents, where used. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing.

Ancillary areas

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

Storage areas

Storage areas were of sufficient capacity. There were separate sampling areas for starting materials and primary packaging materials. Sampling was carried out under laminar airflow.

Weighing areas

Dispensing and weighing were carried out under laminar airflow in individual dispensing booths.

Quality control areas

QC laboratories were separated from production 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. Separate air-handling units were provided for microbiological laboratories.

Pest and rodent control

This area was not inspected in detail, but various traps for rodents and insects were seen at suitable locations at the facility.

2.13 EQUIPMENT

Production equipment

Production equipment was generally found to be in adequate condition.

Air handling units and HVAC

The building management system (BMS): the air handling units were shut down and turned back on, on a regular basis, following intimation requests. Issues were raised which were resolved in CAPAs.

2.14 MATERIALS

As noted during the previous inspection of this site, the incoming materials and finished products were quarantined after receipt until they were released for use or

distribution. Materials and products were generally stored under the appropriate conditions. See the previous WHO inspection report for more details.

2.15 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.

Labels, specifications, master formula, packaging instructions and batch processing/packaging records and standard operating procedures were reviewed. These were generally considered acceptable.

2.16 GOOD PRACTICES IN PRODUCTION

Processing operations

Each granulation area had personnel with different colour coded uniforms. Staff wore two pairs of booties, and the second pair was removed after manufacturing operations of one type before going back into the corridor.

Before processing operations were started, steps were taken to ensure that the work area and equipment were 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

Secondary packaging operations were observed during the verification of the recent complaint for PAS sodium which had been made regarding missing spoons and package information leaflets. The company had procured a camera based system and had changed the design of boxes to have the spoon (now coloured blue instead of clear), be manually inserted in one compartment and the leaflet, now pink, inserted in the other compartment. Contract staff was still being used to perform all of the secondary packaging at the time of the inspection. The instructions were to verify the absence of defects, such as powders trapped in the sealing, inadequately printed lines, etc. Rejected packages were placed in the rejected bin and after examination, these could be defoiled/deblistered and the product reused.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Wet chemistry laboratory

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

All of the systems described to be present were visible on the network at the time of the inspection.

Microbiological laboratory

This area was generally considered acceptable.

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, as well as the corrective actions taken and planned, *Macleods Pharmaceuticals Ltd (block No2) located at Village Theda, P.O. Lodhi Majra, Tehsil Baddi, District: Solan, Himachal Pradesh 174 101 India*, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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.