



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	MacLeods Pharmaceutical Ltd
Unit number	Daman
Production Block	Phase II (Tablets, capsules, Rifampicin and non-Rifampicin as well as SSF)
Physical address	MacLeods Pharmaceutical Ltd, Plot No. 25-27, Survey No 366, Premier industrial estate, Kachigam, Daman - 396 210 (UT), INDIA
Date of inspection	15 to 19 February 2010
Type of inspection	Routine Inspection
Dosage forms(s) included in the inspection	Tablets, capsules and granules
WHO product categories covered by the inspection	Finished Pharmaceutical Products (FPPs) used in the management of Tuberculosis (TB) and HIV/AIDS (HA)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of injectable, tablets, and capsules.



Part 2: Summary

General information about the company and site

MacLeods Pharmaceuticals Ltd was incorporated in 1986. The company runs one site involved in research and development, four manufacturing sites for the finish dosage forms and one site involved in API manufacturing. The product range included anti-TB, anti-malaria, anti-bacterial, anti-retroviral, cardiovascular and proton pump inhibitor medicinal products. MacLeods Pharmaceuticals Ltd. supplies products to the Indian market, to emerging markets (Africa, Latin America, CIS, South-east Asia), markets such as USA, Europe, Canada and Australia as well as WHO regulated markets. The company employed about 5500 members of staff in total. About 120 employees were enlisted at the site inspected (Plot No 24-28, Premiere Industrial Estate, Kachigam, Daman, U.T.). Tablets (coated and uncoated), hard gelatine capsules, granules and dry powder injectable products were manufactured here.

History of WHO and/or regulatory agency inspections

The manufacturing of tablets, capsules and granules departments of this site have been inspected and approved several times by WHO and other agencies including US FDA and MHRA.

Focus of the inspection

The manufacturing of solid dosage forms was not inspected in detail. Only the SSF and Rifa departments in Phase II were inspected briefly. The scope of the inspection of other areas is not presented in this WHOPIR.

The inspection covered various sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

After a brief introduction by all persons attending the opening meeting on the first day, the company gave a presentation covering its activities and changes made since the last inspection. The inspection was started with an overview of the activities involved in the manufacturing of products and followed by a review of several systems and documents.

- Job descriptions reviewed included that of the responsible for batch approval (Deputy General Manager Quality)
- Procedure for Quality Risk Management
- Procedure and Product Quality Review for a selected product
- Deviations register
- Change control register
- Vendor qualification procedure and reports selected
- Qualification and validation status of premises, equipment and processes
- Performance Qualification
- Training of personnel SOP and records

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A summary of the days findings were presented before closing the inspection for the day.

On the second day of the inspection, the inspectors reviewed the site layouts, layout of the premises - including material and personnel flow, pressure cascading, air flow, equipment layout and HVAC systems for the different areas relating to area classification.

After this review and discussion, an on-site inspection of the new warehouse, sampling areas and previously inspected warehouse and dispensing areas was conducted. The areas were inspected, selected documents were reviewed and personnel were questioned regarding the relevant activities in the areas.

After lunch, the inspectors reviewed selected documents including SOPs, records, protocols and reports relating to the qualification and validation of processes and utilities.

A summary of the days findings were presented before closing the inspection for the day.

On the third day of the inspection, the inspectors requested a list of batch records for inspection manufactured in the "new" area. They reviewed documents - including the SOP for transfer of material, the temperature mapping protocol - and then went to the sterile production area. They reviewed some documents on line. After lunch, the inspected selected batch records and batch release.

A summary of the day's findings were presented before closing the inspection for the day.

On the fourth day, more focus was placed on the manufacture of solid dosage forms. After a brief overview on the floor layout, personnel and material flow, AHU's and pressure differentials, the inspection continued on the production area of the SSF department (manufacturing of small size batches of non-Rifa products). During the walk-through - spot checks were carried out covering several activities as well as procedures and records in that area. These included, among others, handling of punches and dies, materials and calibration records. The morning was concluded by inspecting the systems involved in identity testing of sterile APIs and the protocol and report for the process validation for a selected product.

In the afternoon, a walk-through of the area used for manufacturing of Rifampicin containing products was done.

In 2008 the purified water system was modified. The documentation relating to these changes (change request, validation of the purified water system) was checked.

A summary of the day's findings was presented before closing the inspection for the day.

The fifth day was spent inspecting the quality control sections. The inspection covered the chemical, the packaging materials and the microbiology laboratories. Documents reviewed included, among others, procedures and records for finished product and packaging materials testing, the handling of samples and reference standards, preparation of working standards, the signature log, stability studies and spot checks on personnel training. In the microbiology laboratory, the media preparation, the handling of cultures, growth control testing, the loading patterns for the autoclave, the temperature



control of the fridge and incubators as well as the pressure differential log for the area were inspected.

2.1 QUALITY ASSURANCE

There was a quality assurance system in place that covered all the relevant aspects of the WHO GMP guidelines. Production and control operations were specified in written form, deviations were reported, investigated and recorded and changes were approved before implementation. Annual product quality review was done according to an SOP, however, some aspects were not covered fully such as trending of results / data and regulatory parameters. No formal risk management was implemented. These were satisfactorily addressed in the corrective actions provided by the company following the inspection.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general, the main principles of Good Manufacturing Practices were addressed in the quality assurance system. With some exceptions, principles were implemented and followed. Environmental monitoring during manufacturing activities was addressed following the inspection.

2.3 SANITATION AND HYGIENE

In general, a high level of sanitation and hygiene was practised. There were systems implemented to minimize the risk of contamination and cross-contamination to an acceptable level. Cleaning procedures and records for premises and equipment were available. Some of the cleaning procedures were reviewed and updated after the inspection. Cleaning validation was in place.

2.4 QUALIFICATION AND VALIDATION

The validation policy of the company was documented in a validation master plan. The validation master plan also covered cleaning procedures, analytical methods and computerized systems. Protocols and reports for the qualification and validation were available for the premises, utilities, equipment and processes checked during inspection.

2.5 COMPLAINTS

Complaints were handled, investigated and reviewed according to the established procedure.

2.6 PRODUCT RECALLS

Not inspected.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Some analytical testing was contracted out to other parties. The contract checked during inspection did not raise any observations.

2.8 SELF INSPECTION AND QUALITY AUDIT

Not inspected.

2.9 PERSONNEL

An organizational chart was available. Individual responsibilities of key personnel were defined in job descriptions. Quality assurance and quality control departments were independent from production. The head of quality assurance was responsible for the release of products.

2.10 TRAINING

The procedure for training listed the introductory training for new employees as well as the on-going training of existing staff. On-going training was carried out according to a training schedule.

2.11 PERSONAL HYGIENE

Employees had to undergo a health examination prior to employment. The initial training also included aspects to personal hygiene and gowning.

2.12 PREMISES

In general, the premises were found to be designed, constructed, maintained and cleaned to suit the operations carried out. Some of the areas were rather limited in space (e.g. packaging materials store). Maintenance of the premises needed attention - this was addressed through the company's corrective and preventive action. The logical flow of materials and personnel was ensured. The HVAC system was suitably designed, installed and maintained. A new purified water system was installed about three months prior to the inspection and was still under validation (phase III was on-going).

2.13 EQUIPMENT

In general, the equipment was found to be designed, constructed, maintained and cleaned to suit the operations carried out. Cleanliness levels and maintenance was, in general, found to be acceptable. Some minor exceptions were identified during the inspection. These were corrected by the company. The calibration and qualification schedules were up to date (see also chapter on qualification).

2.14 MATERIALS

Flow of materials was in general found to be acceptable. Deviations from GMP were identified in the areas of identity testing of APIs, batch segregation of packaging components, and number of samples tested (primary packaging materials). Material management linked to production planning required attention: These issues were addressed through the company's corrective and preventive action.

2.15 DOCUMENTATION

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The company had an elaborate documentation system with SOPs, specifications, protocols and reports as well as other related documents. These were in general acceptable (clearly designed, completed, controlled and authorized).

2.16 GOOD PRACTICES IN PRODUCTION

In general, production activities were performed in accordance with SOPs and batch documentation as well as principles of GMP.

2.17 GOOD PRACTICES IN QUALITY CONTROL

In general, quality control activities were performed in accordance with SOPs. Traceability to materials used and activities performed during testing was not always ensured. The recording of observations as well as the checking activities by a second analyst required attention - this was addressed through the company's corrective and preventive action..

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 Ltd Plot No. 25-27, Survey No 366, Premier industrial estate, Kachigam, Daman - 396 210 (UT), INDIA was considered to be operating at an acceptable level of compliance with WHO GMP guidelines for OSD forms and granules.

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.

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.