

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Macleods Pharmaceuticals Ltd
Physical address	Village Theda, P.O. Lodhi Majra, Tehsil Nalagarh, District: Solan, Himachal Pradesh 174 101, India
Block	N2
Postal address	As above
Telephone number	HQ: +91-22-6676 2800 Site: +91-1795 661400
Fax number	+91-1795 661452
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of FPP: solid oral dosage forms (tablets and hard gelatin capsules) and liquid oral dosage
Indicate dosage forms and type of products (e.g. tablets; cephalosporin containing products)	Cephalosporin containing and hazardous products were not manufactured at the site
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number	Prequalified product: • TB154: Cycloserine capsules 250mg Products under assessment • TB 218, TB 219, HA 506, HA 513, HA 523 HA 526.
type of inspection	Routine inspection, covering all aspects of GMP
Date of inspection:	20 – 24 February 2012

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh
February 2012

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Part 2: Summary

Background information

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

- Daman - Solid oral dosage forms
- Nalagarh, Himachal Pradesh - Solid and Liquid oral dosage forms
- Palghar, Maharashtra - Solid and Liquid oral dosage forms
- Sarigam, Gujarat – Drug substances

The total number of employees engaged on the site for Production, Engineering, Production Planning and Control (PPC), QC/QA, Stores and Distribution was about 269 employees, In addition, approximately 50 contract employees were in secondary packaging operations.

History of WHO or regulatory agencies inspections

The Nalagarh site was inspected by:

- USFDA
- UK MHRA
- MCC South Africa
- SFDA Saudi Arabia
- INVIMA Colombia
- PPB- Kenya

The last routine WHO inspection at Nalagarh site was carried out in March 2009. In January 2011, WHO inspection team carried out Biowaiver inspection.

Focus of the inspection

The inspection focused on the production and control of prequalified product and products under assessment. The inspection covered all the sections of the WHO GMP text, including Quality assurance, premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control, utilities, manufacture

Inspected Areas

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

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh
February 2012

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

In general a system for quality assurance was established.

Quality Risk Management (QRM)

QRM SOP was reviewed. SOP was based on HACCP and FMEA.

Risk assessment log for 2011 was also reviewed. Nine risk assessment cases have been recorded.

Product Quality Review (PQR)

PQR SOP was reviewed. According to the SOP – all batches manufactured during a calendar year from January to December should be considered for the PQR. PQR reports have been checked by Head of the QC and Head of the production. PQR reports have been approved by the Plant head and the Head of QA.

Change control

Change control SOP was reviewed. Changes were classified as:

- Minor change
- Moderate change
- Major change

Change controls were reviewed and approved by the Corporate QA.

Change control register for 2011, block N2 was checked. There were eighty three documentation and thirteen facility related changes recorded.

Deviation management

SOP and trend analyses were reviewed. Deviations were classified as following

- Critical deviation
- Major deviation
- Minor deviation
- Unplanned deviation
- Planned deviation

Planned deviations – change of compression machines were reviewed

Handling of non-conformances

Non-conformances were reported by department's executives. Non-conformances were defined as unintentional or intentional lack of conformance to approved procedures and systems. The SOP was related to the following items:

- OOS
- OOT
- On line rejections
- Market complaints
- Deviations
- Wrong entry in documents

Corrective and Preventive Actions (CAPAs)

SOP CAPA and CAPA assessment tracking log for 2011 was reviewed. Three CAPA assessment cases have been recorded. CAPA against market complaint was reviewed.

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. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

Clean areas were cleaned in accordance with approved written procedures. Environmental monitoring was regularly undertaken.

2.4 QUALIFICATION AND VALIDATION

The company identified what qualification and validation work was required. The key elements of the qualification and validation programme were defined in the validation master plan (VMP).

Validation Master Plan

VMP was spot checked. The VMP was applicable for:

- Process validation
- Cleaning validation
- Control system validation
- Utilities validation
- Analytical method validation
- Vendor qualification

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh
February 2012

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

- Documentation and support systems

Process validation

A specific process validation protocol & report as well as Batch Manufacturing Records (BMR) and Batch Packaging Records (BPR) were reviewed.

BPR of a specific suspension was checked and rejected amount of suspension was recalculated. Cleaning and dispensing labels were added to the BPR.

Cleaning validation

Cleaning SOP and product list was reviewed. Cleaning validation was based on “worst case product” approach. Validation studies were carried out using swab samples and rinse samples. Swab recovery studies have been carried out for:

- Teflon surface
- SS surface
- Silicon surface

Minimum swab recovery was specified not less than 80%.

A cleaning validation protocol was reviewed.

A cleaning validation report for tablet manufacturing equipment was reviewed.

Cleaning verification SOP was checked. Cleaning effectiveness verification was carried out after each tenth change over e.g. after tenth consecutive type B cleaning and involved visual evaluation of the equipment and also swab samples.

Hold time study for a specific product was spot checked.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written procedure. Complaints concerning a product defect were recorded and investigated. Consideration was given to whether other batches should be checked in order to determine whether they were also affected. Complaints records were part of the Batch manufacturing and packaging records.

The head of QA was responsible for handling of the complaints.

Customer complaint register for 2012 was checked.

Specific complaints were reviewed. During inspection one complaint was open and investigation was going on. Customer complaint register for 2011 was also checked.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was reviewed. The Head corporate QA was responsible for the execution and coordination of recalls. There were voluntary recall and forced recall.

Recalls were classified as:

- Class I
- Class II
- Class III
- Caution in use

According with the SOP mock recall shall be carried out once in two years. Domestic market mock recall was carried on 25 March 2010; export Market mock recall was carried out on 6 April 2010. Till the date of inspection there was no product recalls.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production operations were not contracted out. Some analytical tests were contracted out to two contract laboratories. Technical Agreements with these laboratories were reviewed and were generally satisfactory.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were performed routinely. Self-inspection covered basic GMP topics.

Self-inspection team was defined and leaded by the QA personnel at least twice per year for all departments. Audit schedule was available and was checked. Audit was carried out according with check list for every department. Deficiencies/observations were classified as following:

- Critical
- Major
- Minor

Self-inspection report was prepared by the QA executive. Head of the audited department should submit CAPAs. CAPAs were approved by QA and lead of inspection team. If required, follow up audit was carried out.

Vendor qualification and approval

Vendor qualification and approval was Corporate QA responsibility. Approved vendors lists for starting materials and packaging materials were available. Audits were carried out mainly for API vendors.

According with SOP audits should be carried out every three years.

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. Responsible staffs, specific duties were recorded in written job descriptions. Key personnel deputies were identified in job descriptions. Personnel 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. An organization chart was available - and was appropriate.

The following Job descriptions were reviewed:

- Assistance general manager – QA
- Assistance general manager - Production
- Deputy General Manager – Quality Control

2.10 TRAINING

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories.

Training SOP was reviewed. There were following typed of training:

- Induction training
- On-job training
- Annual training programme as per annual training calendar advanced training

Training manual and training modules were presented to the inspectors. Seventeen training modules were available.

Management training files were kept by individuals, operators training files were kept by the training coordinator of particular department.

Training effectiveness was evaluated by the descriptive questions and already given answers. This system applied for management staff and officers. Operators training were evaluated by verbal questions and discussions at the end of the training session. Training was recorded in the training attendances and evaluation sheets.

Site employed around fifty contract workers to carry out secondary packaging operations. GMP training module and “Do’s and don’ts” in production areas were available in local language. Training for the contract workers on the subject “Do’s and don’ts” in production areas was carried out on daily basis. Training records were presented to the inspectors. Training records identified only contract workers first names and employee card numbers, surnames were not identified.

2.11 PERSONAL HYGIENE

Periodic health checks were carried out for staff workers and senior management. SOP Procedure for Medical check-up was spot checked. Contract with labour supply agency was also spot checked.

Changing and washing followed 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 was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not allowed in clean areas.

2.12 PREMISES

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. Changing rooms were equipped with mirrors and photographs showing gowning procedures. Airlock doors did not open simultaneously.

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 were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products. There were separate sampling areas for starting materials and primary packaging materials. Sampling was carried out under reverse laminar airflow.

Weighing areas

Dispensing was carried out in the warehouse in two separate dispensing booths. Dispensing was carried out under laminar airflow.

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

SOP, observation of rodent traps & gum pads and contract with service provider was reviewed. Pest and rodent control was carried out by contract agency.

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh

February 2012

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

2.13 EQUIPMENT

Fixed pipework was clearly labeled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments suited to the testing procedures undertaken.

Equipment was subject to planned preventive maintenance and calibration. Frequencies of PPM and calibration were generally satisfactory and the schedule was routinely achieved.

SOP “Operation and Cleaning of Sampling booth/area (Raw material)”, SOP “Cleaning and operation of manufacturing tank”, SOP “Cleaning Procedure of Lube transfer Pump” and SOP “Cleaning and operation of process line in liquid orals” were reviewed.

Extensive HVAC systems were installed, with 82 separate units. Each unit contained appropriate filters, finishing with a 0.3 micron HEPA filter in manufacturing areas.

Air quality reports for Granulation area II and compression room II were reviewed and appeared generally satisfactory with grade D quality routinely achieved.

PPM for filter cleaning and changing was reviewed and was generally satisfactory.

Purified water was generated from bore well supply through a double pass RO system followed by an EDI system. Purified water was continuously circulated in a stainless steel loop at ambient temperature. Tank and loop were routinely sanitised by heating to 83 degrees C for 1 hour. RO membranes were also routinely sanitised at 60 degrees C. The systems appeared well constructed and controlled.

Compressed air was supplied from an oil free system. Appropriate filters were installed in the system, ending in 0.1 micron filters at point of use.

Nitrogen was generated from an Alumina bed system and again 0.1 micron filters were installed at point of use.

2.14 MATERIALS

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under the appropriate conditions.

Starting materials

Starting materials were purchased from approved suppliers. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material was recorded and

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh

February 2012

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

reported to the QC department. If one delivery of material was made up of different vendor batches, each batch was considered as separate for sampling, testing and release. Starting materials in the storage area were appropriately labeled.

There were appropriate procedures in place to ensure the identity of the contents of each container of API. Bulk containers from which samples were drawn were identified.

SOP “Code to code transfer of raw materials” was reviewed.

Packaging materials

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure conditions. Each delivery of batch of printed or primary packaging material was given a specific reference number or identification mark.

Intermediate and bulk products

Not inspected

Finished products

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer.

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were marked as such and stored separately. Product was claimed to not be reprocessed or reworked. However acceptable minor reprocessing such as de-blistering of tablets from foils was performed.

Recalled products and Returned goods

Secure space was provided for storage of recalled and returned goods.

Reagents and culture media

Records for the receipt and preparation of reagents and culture media were available. Reagents made up in the laboratory were prepared according to written procedures and appropriately labeled. Growth promotion tests were carried out.

Reference standards

Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were properly labeled and stored. Working standards were dispensed in 13 amber vials for individual use. Dispensing was carried out under RLAF. The temperature in the reference standards storage fridge was monitored.

Waste materials

Not inspected

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

In general labels applied to containers, equipment and premises were clear and unambiguous. However some containers were seen not properly labeled.

Specifications and testing procedures

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

Master formulae

Authorized master formulas were available.

Packaging instructions

Authorized packaging instructions were available.

Batch processing records

Batch manufacturing records (BMRs) were kept for each batch processed. Before any processing begins, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded and were part of the BMR.

Batch packaging records

A batch packaging record (BPR) was kept for each batch processed. Before any packaging operation begins, checks were made that the equipment and work station were clear of previous products, documents or materials, and that equipment was clean and suitable for use.

Standard operating procedures and records

SOPs and associated records of actions taken were available.

Assessment of the Site Master File

The Site Master File was available in electronic form before the visit was made to the manufacturing site. In general it complied with the guidelines on preparation of the SMF.

2.16 GOOD PRACTICES IN PRODUCTION

Handling of materials and products was carried out in accordance with written procedures. Checks on yields and reconciliation of quantities were carried out.

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh

February 2012

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

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. The line clearance was performed and recorded in BPR, except for secondary packaging operations where line clearance was recorded in a separate log book. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

2.17 GOOD PRACTICES IN QUALITY CONTROL

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

Sampling

SOP “Sampling, testing, review, release and rejection of raw materials” was reviewed. Starting materials excipients and API were 100 % sampled for identity tests. Identity tests were carried out on individual samples. Maximum of five samples of API were used for composite sample.

SOP “Sampling, testing, review, release and rejection of packaging materials” was reviewed. Acceptance Quality Level (AQL) was applied for the sampling of packaging materials.

Packaging materials defects were defined as:

- Critical
- Major
- Minor

Control of starting materials and intermediate, bulk and finished products

Tests followed the instructions given in the relevant written test procedure. The tests results were recorded in Analytical data sheets. Tests results were checked by the Head of the section and approved by the Head QC before the material or product was released. Out-of-specification results and out of trend results (only for stability tests) obtained during testing of materials or products were investigated in accordance with an approved procedure. Records were maintained. Laboratory Incidents were recorded separately to OOS.

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh

February 2012

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

Test requirements*Starting and packaging materials*

Before releasing a starting or packaging material for use, the QC Head ensured that the materials have been tested for conformity with specifications. An identity test was conducted on a sample from each container of starting material. Each batch of printed packaging materials was examined following receipt.

In-process control

In-process control records were maintained and formed a part of the batch records.

Finished products

For each batch of medicines product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

Batch record review

QC records were reviewed as part of the approval process of batch release.

A specific product analytical data sheet and CoA was spot checked.

Retention samples

Retention samples from each batch of finished product and API, as well as related documents were kept for one year after the expiry date. Finished products were kept in their final packaging and stored under the recommended conditions. Retention samples were stored under appropriate conditions.

Stability studies

A written programme for ongoing stability determination was developed and implemented.

SOP Stability studies, Master stability study plan for February 2012 and stability sample analysis record were spot checked. On spot checks, stability study Master plan was followed.

Stability and on-going stability samples were stored properly. Temperature in the room was continuously monitored. Incubators were equipped with alarm system.

Validation of Analysts

SOP Validation of Analyst was spot checked.

New analysts were given coded, previously analysed samples for their validation test. The tests procedures for the test parameters involved (one or more) of the following methods of analysis:

- HPLC
- UV

WHOPIR:

Macleods Pharmaceuticals Ltd Nalagarh
February 2012

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

- Auto-titrator
- KF analysis
- IR spectrophotometry

Acceptance criteria for each test were specified.

A specific analyst validation report and analyst instrument testing matrix was spot checked.

Microbiological laboratory

SOP Procedure for Microbial Air Monitoring and trends for 2011 was spot checked. Settle plates were exposed for 4 hours. Action and alert limits were specified. Monitoring was carried out on weekly basis for each sampling point. In manufacturing areas, settle plates were exposed in front of the return air grills and also at other specified spaces. Environmental isolates were identified. Active air sampling was carried out fortnightly. 1000 l of air was taken for the monitoring.

Settle plate exposure time validation studies - the document “To study growth promoting property of media after exposure to environment” was spot checked.

SOP Sampling and monitoring of Purified water and trends for 2011 was spot checked. Action and alert limits were specified. Each sampling point was covered weekly.

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 (block No2) located at Village Theda, P.O. Lodhi Majra, Tehsil Nalagarh, 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.