World Health Organization

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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Macleods Pharmaceuticals Limited**
Corporate address of the manufacturer	Macleods Pharmaceutical Limited, Research & Development Centre, G-2, Saket Bldg., Near Onida House, Mahakali Caves Road, Andheri (E) *Mumbai, India. 400093*
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Macleods Pharmaceuticals Limited Block-N2, Village – Theda, Tehsil Baddi, Himachal Pradesh, India
Unit/block/ workshop number	Block-N2 General block (GB-1, GB-2 and GB-3)
Inspection details	
Dates of inspection	7-11 November 2022
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Macleods Baddi (Unit VI) identified as Block N2 (General Block) having three separate blocks as 1. General Block -1 (Solid orals and liquid orals) (GB1) 2. General Block -2 (Solid orals) (GB2) 3. General Block-3 (Solid orals) (GB3). The Baddi (Unit VI) has two independent manufacturing facilities, the Foil Printing Unit and the Carton Printing Unit, within a common premise. 1. Block N1 (Small Tablet and Soft Gelatin Block). 2. Block N2 (General Block) 3. Foil Printing Unit 4. Carton Printing Unit
General information about the company and site	Macleods Pharmaceuticals Limited was established in 1986. Macleods manufactures and markets a wide range of pharmaceutical formulations from Tablets to sterile dosage forms and from inhalation to novel drug delivery systems. It is engaged in the manufacturing of both, primary and secondary anti-Tuberculosis formulations. Macleods is a vertically integrated global pharmaceutical company. The company has the following manufacturing

	facilities across India: 1. Pharmaceutical Formulation (Unit I), Palghar, District: Thane, Maharashtra INDIA 2. Pharmaceutical Formulation (Unit II), Daman (Union Territory) INDIA 3. Pharmaceutical Formulation (Unit III), Kabra, Daman (Union Territory) INDIA 4. Pharmaceutical Formulation, Foil Printing (Unit VI), Baddi, Himachal Pradesh INDIA 5. Pharmaceutical Formulation (Unit VII), Daman (Union Territory) INDIA 6. Pharmaceutical Formulation (Unit IX), Sikkim INDIA 7. Pharmaceutical Formulation (Unit XI), Pithampur, Madhya Pradesh INDIA 8. API Manufacturing Facility & Pharmaceutical Formulation (Unit V), Sarigram, Gujarat INDIA 9. Research and Development (R&D) centre, Mahakali Caves Road, Andheri, Mumbai INDIA 10. Foil printing Unit, Daman (Union Territory) INDIA 11. Carton Printing Unit, Baddi, Himachal Pradesh INDIA 12. KSM / Intermediate, Unit X, GIDC Dahej, District: Bharuch, Gujarat INDIA
History	Macleods Baddi site (Unit-VI) has been regularly inspected by the WHO Prequalification Inspection Services. The last WHO PQ inspection was conducted in October 2019.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The following areas were inspected: - Pharmaceutical quality system - Personnel and training - Documentation - Hygiene and sanitization - Process and computerized system validation - Equipment - Production and packaging - Quality control laboratory - Validation and qualification - Utilities
Restrictions	None
Out of scope	The inspection was limited to Block-N2 covering General Block (GB-1, GB-2 and GB-3) where Prequalified Products were produced. Products and facilities not related to the WHO Prequalification Program were out of the scope of this inspection and hence not inspected.
WHO products covered by the inspection	1. TB154 Cycloserine Capsules USP 250mg 2. TB156 Para Aminosalicylate Sodium delayed-release granules 60g/100g 3. TB179 Isoniazid Tablets 300mg

		4. TB230 Moxifloxacin (as Hydrochloride) 400mg Tablets
		5. TB277 Levofloxacin Tablet, Film Coated 250mg
		6. TB278 Levofloxacin Tablet, Film Coated 500mg
		7. TB279 Levofloxacin Tablet, Film Coated 750mg
		8. TB297 Linezolid Tablet, Film-coated 600mg
		9. TB307 Pyrazinamide Dispersible Tablets BP 150mg
		10. TB326 Levofloxacin Tablet, Dispersible 100mg
		11. TB342 Moxifloxacin (hydrochloride) Tablets, Dispersible 100mg
		12. TB390 Bedaquiline Tablets 100mg **(under assessment)**
		13. HA424 Lamivudine Tablets 150mg
		14. HA459 Lamivudine 150 mg and Zidovudine 300mg Tablets
		15. HA506 Efavirenz Tablets 600mg
		16. HA514 Lamivudine/Tenofovir DF, Tablets Film Coated 300mg/ 300mg
		17. HA516 Tenofovir Disoproxil Fumarate Tablets 300mg
		18. HA523 Lamivudine Oral Solution 10mg/ml
		19. HA526 Zidovudine Oral solution 10mg/ml
		20. HA561 Emtricitabine / Tenofovir DF Tablet, Film coated 200mg / 300mg
		21. HA562 Efavirenz/Emtricitabine/Tenofovir DF, Film-coated Tablets, 600 mg/200 mg/300 mg
		22. HA573 Lopinavir Ritonavir Film Coated Tablets 100mg/25 mg
		23. HA574 Lopinavir Ritonavir Film Coated Tablets 200mg/50 mg
		24. HA611 Efavirenz Lamivudine/Tenofovir disoproxil fumarate - 600mg/300mg/300mg Tablets
		25. HA713 Dolutegravir (Sodium)/Lamivudine/ Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg
		26. HA714 Efavirenz/Lamivudine/ tenofovir disoproxil fumarate Tablet, Film-coated 400mg/300 mg /300 mg
		27. HA735 Sulphamethoxazole and Trimethoprim Tablets 400mg/80mg

	28. HA736 Sulphamethoxazole and Trimethoprim Tablets 800mg/160mg
	29. HA740 Abacavir/Lamivudine Tablets 600mg/300mg
	30. HA765 Dolutegravir Dispersible Tablets 10mg
	31. MA176 Primaquine tablets 15mg **(under assessment)**
	32. DI005 Zinc (as Sulfate monohydrate) 20mg Tablets
	33. NT004 Praziquantel tablet, Film-coated 600mg
	34. IN014 Oseltamivir (as phosphate) Capsules, hard 30mg
	35. IN015 Oseltamivir (as phosphate) Capsules, hard 45mg
	36. IN016 Oseltamivir (as phosphate) Capsules, hard 75mg

Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar airflow

LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non-conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments (where applicable)**

1. Pharmaceutical quality system

The site had a formal documented quality system that met most of the requirements of the current WHO GMP Guidelines. The QA and production departments were independent of each other, and both QC and QA reported to Corporate QA. The policies, master files and procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Product and processes were monitored, and these results were considered during batch release. At the time of the inspection, some elements of the quality management system were managed through the track-wise system which included change control, out-of-specification and out of trends, CAPA, deviation and market complaints. The following quality system elements were reviewed.

Product quality review (PQR)

A site-specific procedure was in place applicable to the N2 block only. The procedure described the objective, scope, responsibility, and procedure for carrying out the PQR. The data from each batch is fed back into the PQR module of the ERP system by the QC and reviewed by the QA (senior executive QA). It is a rolling review as data are fed into the system concurrently. The PQR was performed for all products including commercial and those under assessment. The procedure covered all aspects of the products including commitment, stability, and the recommendation from the previous PQR. The statistical data interpretation was performed using ±3 sigma. The company have recently initiated a CAPA to start calculating process capability.

Change management system

The SOP on change management system laid down a procedure for initiation, approval, execution of changes, roles & responsibilities and requirements for the management of changes as per cGMP through TrackWise software. The procedure applies to new product introduction, technology transfer, the extension of product from one market to another market, change in raw materials & packaging materials, addition or deletion of approved contract laboratories, addition or removal of any new equipment, area modification, document revision etc. The changes were classified as minor, major and critical and the cross-functional team was responsible for reviewing the proposed changes. A risk assessment was performed based on the impact of the proposed change and regulatory approval was sought before implementation. Change control effectiveness was assessed for all changes except for pre-submission products. In general, the procedure was found adequate.

Deviation Management

The SOP Event Management was reviewed. The purpose of the procedure was to provide a systematic, standardized and effective approach to report all noncompliance failures and perform root cause analysis to deliver a robust solution to the identified issues on time. Events were classified as critical, major and minor. The categorization includes incidents which may not require an investigation and an event that still requires investigation. The purpose was for the root cause to be established as well as corrective action and preventative action. The originator created the event record within TrackWise. The details in the event record included Product quality Impact, Process performance impact, GMP impact, Yield Impact, Qualification Impact, Calibration Impact, Validation Impact, Training Impact, Impact on other documents, and Impact on equipment, Instruments or Systems. Two Risk models were used:

- FMEA (risk categorization) and
- HACCP (risk Categorization)

Quality risk management

The SOP on quality risk management guided objectives, scope, responsibility, definitions and procedures. The procedure stated that QRM is part of integrated quality management which includes quality defects, auditing & inspection, and periodic review. The procedure stated that risk should be reviewed once every 2 to 3 years. The company should ensure that risk assessment is current and adequate controls are implemented. The procedure was based on ICH Q9 principles and included the use of various tools such as FMEA, FMECA, FTA, HACCP, and HAZOP, besides flowcharts, check sheets, process mapping and fish and bone diagrams. The risk priority number was calculated using severity, occurrence and detection. The procedure also stated that periodic risk reviews are to be performed once every two years for DIRA and cross-contamination whereas three years for QMS-related risks.

The data integrity policy was approved by the QA Head and by the Managing Director of the company. The policy was drafted based on the USFDA, UKMHRA and other guidelines.

Antimicrobial resistance
The company has introduced a new procedure for handling antimicrobials.

The deficiencies noted from the pharmaceutical quality system section have been addressed satisfactorily and the same will be verified during future PQ inspections.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were defined in standard operating procedures. Manufacturing and packaging steps were adequately defined in batch manufacturing records and batch packaging records. The storage and distribution of products ensured batch traceability from receiving to final product and testing. Required resources were available, including adequate premises, equipment, and utilities. Appropriately qualified personnel were employed and in general, training was performed. Qualification and validation were performed following approved protocols.

Macleods Pharmaceuticals Limited, Baddi Unit-VI (especially all three general blocks, GB-1, GB-2 and GB-3) is a multipurpose manufacturing facility which produces pharmaceutical products for different therapeutic areas.

The deficiencies noted from the GMP for the pharmaceutical products section have been addressed satisfactorily and the same will be verified during future PQ inspections.

3. Sanitation and hygiene

The level of sanitation and hygiene was generally satisfactory. The company had standard operating procedures as the basis for its approach to personal hygiene and sanitation in its production facilities. There was appropriate gowning for both staff and visitors including pictorials and provision for hand sanitization before entry to production areas. Cleaning tools and agents were available. Classified areas were cleaned frequently following an approved written programme.

4. Qualification and validation

The validation master plan (VMP) was updated every year before the start of a new year and it identifies areas, equipment, and utilities to be validated following the respective procedures and protocols. The VMP covered the qualification of equipment/instruments, process validation, AMV, CSV, HVAC, transport validation, vendor validation, inspector validation and other areas. The process validation was carried out using three stages; namely process design, process qualification and continued process verification. The cleaning validation refers to the use of 10ppm, dose criteria besides the PDE approach. The cleaning validation was revised for PDE criteria and implemented in November 2022. In general, the VMP has identified qualification and validation requirements for the facility, utilities, equipment, processes, and methods.

Computerised systems

A periodic review planner for GxP computerised systems for quality control, production and utility department was available. The planner provided the name of the system/application, version number, connection to a specific equipment/system, supplier name, review frequency, initial validation, last periodic review and next periodic review date. The company have performed a gap assessment of all the computerised systems as per the current regulatory requirement, including the ISPE GAMP5 and categorised equipment/system in four categories. The review frequency was determined accordingly.

Cleaning validation

Following the USFDA inspection in Oct/Nov 2021, the company hired a consulting firm "Quality Executive Partners, Inc" to perform a cleaning validation assessment. A remote assessment report of the cleaning validation program was provided. Based on the assessment report provided by the consulting firm, the company have revised their cleaning validation procedure including an approach using a risk-based approach. The cleanability study was performed by taking swab samples from the surface of the equipment as part of the analytical method validation.

Analytical method validation

The analytical method validation related to some of the products was verified and found adequate.

The deficiencies noted from the qualification and validation section have been addressed satisfactorily and the same will be verified during future PQ inspections.

5. Complaints

The Complaints SOP "Handling of Customer Complaints in TrackWise" was reviewed. The purpose was to lay down a procedure for receipt, investigation, communication and trending customer complaints. Departments having defined responsibilities include Pharmacovigilance, Corporate QA, Site QA, Concerned Departments, and Macleods US. Complaints could be customer complaints, Product Quality Complaints, Packaging Defect Complaints, ADR, Counterfeit, Falsified Medicine, Complaints related to distribution, Field Alert, and Health Hazard Assessment. Corporate QA was to log the complaint within one day and acknowledge the complaint within two days, creating a complaint in TrackWise. Complaints were categorized as critical, major and minor.

The deficiencies noted from the complaints section have been addressed satisfactorily and the same will be verified during future PQ inspections.

6. Product recalls

The procedure for product recall overseas market was reviewed. The purpose of the SOP was to lay down a procedure for prompt and effective recall of known or suspected defective products. There were voluntary recalls and statutory recalls. Voluntary recalls were initiated by the licensee/manufacturer as a result of abnormal observations in product quality which could include complaints, deterioration of quality, safety and efficacy including adverse drug reactions, mislabeling, pharmacovigilance, retention sample inspection, and out-of-specifications. Statutory recall was triggered in response to or mandated by the Drug Regulatory Authorities.

The deficiencies noted from the product recall section have been addressed satisfactorily and the same will be verified during future PQ inspections.

7. Contract production, analysis and other activities

The WHO Prequalified and under-assessment products are manufactured at Baddi (Unit-VI) without being contracted out to any third parties. Some of the laboratory tests are contracted to the other laboratories. This section was not inspected in detail due to time constraints.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-Inspection Program

The self-inspection procedure was reviewed. The objective was to lay down a self-inspection procedure for verification of effective implementation of the Quality Management System in adherence to cGMP including Planning and co-ordination of a self-inspection program with corrective and preventative actions. Inspections were performed as Level 1 (intra-department) and Level 2 (inter-department). SOP applied to all of Macleod's units and Oxalis Labs including Dispensing, Manufacturing, Packaging, QC, QA, Engineering/Utility, Microbiology, IT, Warehouse, HR, Personal Administration, Security, Environment Health and Safety.

Audit Frequency

Level 1 Inspection was in place for daily observations, weekly surveys or walk-through analyses in respective departments formally once every 3 months. The Internal Audit by cross cross-functional team was conducted half yearly. The observations were classified as critical, major, and minor. The deficiency report was issued within 7 days and CAPA close out was targeted at 30 days with an option of extension for effective CAPA close out.

Vendor qualification and approval

The vendor qualification and approval procedure were discussed. The vendors were qualified using a questionnaire and on-site assessment (APIs and primary and printed packaging materials). Based on the criticality of the materials, reassessment was performed once every 2 year to 4 years. A separate checklist was used for raw materials (APIs and excipients) and packing materials. A comprehensive list was used to obtain initial information from the supplier. It is recommended to seek more information on the types of materials produced/handled on-site.

The deficiencies noted from the self-inspection, quality audit and supplier approval have been addressed satisfactorily and the same will be verified during future PQ inspections.

9. Personnel

Organograms were reviewed and versions were controlled and referenced to SOPs. The roles and separation between production and QA were adequately depicted on the site organogram. In addition to having a separate site QA head, the site QC head reported directly to the Executive VP of Corporate quality. The quality control activities were also overseen by the laboratory quality assurance who reported to the site QA head.

The deficiencies noted from the personnel section have been addressed satisfactorily and the same will be verified during future PQ inspections.

10. Training

The SOP for the training program through the Pharmaceutical Learning Management System (PLMS) and manual System covered induction program, induction training, on-job training, advanced training and mandatory (scheduler) training were discussed. The training was imparted through self-reading and classroom and criteria of NLT 80% was set for the staff members. The trainers from each department were identified based on their experience and training. The PLMS have been in use since 2019 and it was validated with the support of the supplier. An annual training calendar or schedule for 2022 was available. The training modules on cGMP and data integrity were briefly reviewed.

The deficiencies noted from this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

11. Personal hygiene

In general, the procedures on health and hygiene were followed and new personnel and medical examinations were foreseen before joining the company. In general, the personnel gowning procedure was appropriate however, further improvements are required to ensure the appropriate quality of gowning was worn by the operators. For production areas, a full one-piece suite (boiler suit) was donned, over primary gowns together with shoe covers, head covers as well as masks. The gowning was changed once every day. No evidence of eating and smoking was observed in primary areas.

12. Premises

The facility was situated in a pharmaceutical industrial area. Generally, the layout of the premises was adequate; however, production cubicles such as granulation, blending, compression and primary packaging were not provided generally with separate material and man airlocks. Secondary packaging entrance and gowning were separate. The entrance to the plant was via an unclassified corridor. The linen room issued clean gowns to the operators who, according to the company, changed the gowns daily. Gowning rooms were areas where the change from street clothes to plant clothes occurred.

The primary packing of DLT was inspected. The packing was preceded by bottle cleaning. The clean bottles are transferred via conveyor to the packing line where a desiccant is added before filling. IPC was conducted hourly for correct count, and cap torque. There was a metal detector in line on the packing line. In terms of the camera system, it was challenged at the start of the run and every 4 hours as well at the end of the batch. The capper was an induction sealer and after capping, the sealed container travelled through the mouse hole to secondary packing. For the secondary packing, in terms of splicing, the operator attaches the label both before and after the splice in BPR. The camera system was challenged at the start, every 4 hours and at the end of the run. Tests included 2D code defacing, lot number defacing, and barcode defacing. Missing leaflets were detected by the in-line checkweigher.

The incoming materials were received from the receiving bay after initial verification of the materials through the approved vendor list. The warehouse area located in GB-2 was found clean and tidy at the

time of inspection. It was noted that pellet cleaning was carried out after dispensing the entire batch/material whereas the area was daily cleaned, and racks were cleaned once every 15 days. At the time of the inspection, incoming materials (silica gel sachets) were being unloaded at the receiving area. The receiving bay was equipped with canopy and rodent boxes. Incoming materials were verified for weight with a limit of +/-2%. Although the warehouse was part of the GB-2, it also stores materials required in the GB-1 area. The area was equipped with two sampling and three dispensing areas. The APIs and excipients were 100% sampled for identification using NMR or IR. A pooled sample was prepared using the US military standard. The area was maintained at 20±5°C and less than 60% relative humidity. The company confirmed that all store areas were temperature mapped and thermohygrometers were used for daily monitoring of temperature and relative humidity. The ERP system was used for material inventory purposes and labels were printed from the system and manually pasted on each container. A separate MAL and PAL were provided for both sampling areas. 1st floor housed the primary packaging materials, and the sampling area was equipped with separate MAL and PAL. Printed foils were 100% sampled whereas PVC/PVDC, aluminium and bottles were sampled using the US military standard.

The deficiencies noted from the premises section have been addressed satisfactorily and the same will be verified during future PQ inspections.

13. Equipment

Manufacturing equipment was generally appropriately installed. Preventative maintenance was performed following written procedures. At the time of the inspection monitoring of preventative maintenance activities was performed via a manual system and records were available and reviewed. Equipment history cards were used to record preventative maintenance and breakdown of equipment.

The deficiencies noted from the equipment section have been addressed satisfactorily and the same will be verified during future PQ inspections.

14. Materials

Incoming materials (active, excipients) were received through a receiving bay whereas primary packaging materials were received through a dedicated receiving bay. The receiving bays were equipped with trap stations used for rodent bait. It was noted that the company had separate sampling and separate dispensing areas for sampling and dispensing activity. Sampling for APIs was performed on 100 % of containers whereby the ID testing would be performed on each container.

The deficiencies noted from the materials section have been addressed satisfactorily and the same will be verified during future PQ inspections.

15. Documentation

In general, the documentation system was satisfactorily established and maintained; documents were approved, signed, and dated by appropriate responsible persons, reviewed, and kept up to date. Specifications and testing procedures were available.

The deficiencies noted from the documentation have been addressed satisfactorily and the same will be verified during future PQ inspections.

16. Good practices in production

Clean areas for the manufacture of non-sterile OSD products were classified (ISO 8) and were a multi-product facility. The General Block (GB) is further divided into three subblocks namely GB-1, GB-2 and GB-3. The GB-1 was not inspected during this inspection.

GB-2

The production area was equipped with primary and secondary change rooms (separate for male/female/visitors) and washrooms. Lockers were provided for the staff members to store their street clothes before entering the production areas. Boiler suits were provided for the staff members coming in contact with the products (working in the core processing areas). The entire GB-2 was divided into three floors (a) the ground floor has four bulk packing lines, two blister lines and a quarantine and semi-finished area (b) the first floor has seven compression machines, one capsule machine and five coaters and granules were charged through gravity from the second floor and (c) the second floor has six wet granulation areas, one roll compaction, three blending and three sifting/milling areas

GB-3

Both inspectors visited GB-3 and inspected manufacturing activities including the male change room, granulation, and compression area. The GB-3 facility was spread across three floors (ground floor, first floor and second floor). The ground floor comprises the warehouse (receiving, dedusting, weight verification, undertest and approved area for raw materials) and primary packaging materials store, sampling, and dispensing activities (at the time of the inspection, there were no sampling and dispensing activities carried out). The second floor comprises compression and coating areas and the third floor comprises granulation (including RMG, FBD, blending, and sifter/milling). The equipment were generally not dedicated and manually cleaned in the washing area using high-pressure washing equipment. Cleaned and dried equipment were bagged and stored in separate clean parts storage areas. Checks on sieves and other equipment were regularly performed and were found to be in adequate condition. FBD filter bags and compression tools were dedicated and marked as such and stored in a secure equipment storage area. There were operating procedures in place for checking the integrity of filter bags. The company informed that all three granulation areas will be used for WHO products whereas data submitted from exhibit batches were produced in the pilot area.

The deficiencies noted from the production section have been addressed satisfactorily and the same will be verified during future PQ inspections.

17. Good practices in quality control

The quality control laboratory was located on the 1st and 3rd floor of the administration building. The laboratory has around 400 staff members responsible for testing materials, in-process, and finished products. The laboratory was spread over two floors, the first floor was mainly used for testing finished products whereas the second-floor laboratory was used for testing raw materials, packaging materials and stability samples. There were separate rooms for instruments e.g., balance room etc., chemical analysis and washing/cleaning. Samples were received through a pass box and logged manually. The entrance to the laboratory was through separate change rooms for chemistry and microbiology laboratories.

Manual logbooks were used to log in samples received from the IPQA with requests for testing. The Document Management System (DMS) was used to request an Analytical Datasheet from the QA. The DMS had been in use for 1 year and claimed to be validated. A unique ID (employee code) and password were used to access DMS. The chromatographic data systems (such as HPLC, GC and IC) were operated using Chromeleon 7.2 and connected to a server. In addition, standalone computer systems were in use for equipment such as LCMS, Malvern Mastersizer, dissolution apparatus, Karl Fischer, and analytical balances. The FTIR and UV-VIS were controlled through LabSolution. In addition to having routine QC controls, the laboratory was supported by the laboratory QA team who reported to the site QA Head.

Out of Specifications and Out of Trend

The SOP Handling of OOS/OOT/Atypical Investigations was reviewed. References included ICH Q10, MHRA guidelines on OOS, and FDA Guidelines on OOS. According to the SOP for OOS, an OOS should be investigated immediately and if more than a 24-hour delay, an event was logged in the investigation log with rationale. The methodology: Phase 1 Laboratory Inspection leading into Phase 1a and Phase 1b. Phase 2 was divided into phases 2a and 2b. 2a was production, manufacturing investigation and 2b (hypothesis testing) Prepared solution stability was available for all samples and standards.

Stability studies

The SOP on stability studies provided guidance on the conditions, timepoint, charging within 30 days from the release date, and withdrawal and storage of stability samples. Currently, a manual system is in place (form being used) to track stability time points scheduled for testing. The company is planning to implement a stability study module in the LIMS. It was confirmed by the company that there was no backlog from stability samples. The staff strength of the stability lab was around 125. The stability study of one product was reviewed and noted that the stability study was continued for 60 months at 25°C/60% and 30°C/65% on three batches. The stability study of another product was discussed. The stability study has been completed for up to 36 months.

Microbiology laboratory

The microbiology lab was briefly visited and noted that it comprised 20 microbiologists. The laboratory performs environmental monitoring, water, microbial limit test, compressed air and nitrogen testing (no sterility and BET). The cultures or microorganisms were handled under biosafety cabinet Class-II whereas laminar airflows were used for microbial limit testing. Separate MAL (pass-box)/PAL was provided. A library of environmental isolates was maintained. The environmental monitoring was performed once every month for Grade D areas using passive air sampling whereas the area was requalified using both active and passive air sampling. Dehydrated media was stored appropriately and subjected to a growth promotion test in the first bottle of every batch. A double-door autoclave was used wherein media and other articles were loaded from a controlled but unclassified area and unloaded from

the Grade C area. The autoclave was subjected to a vacuum leak test and bowie dick test daily. Also, the micro lab was equipped with walk-in incubators (22.5±2.5°C and 32.5±2.5°C) and two manual colony counters used for counting the colony-forming units.

Packaging materials

Sampling, testing, releasing and rejection of packaging material were discussed. 100% sampling was performed on primary and secondary packaging materials as per the ANSI/ASQ Z1.4-2003. Packaging material specification for containers was discussed. The packaging materials were tested on-site in the packaging material laboratory located in the warehouse as well as in the main laboratory. The tests such as description, check for contamination, dimensions, overflow capacity, the weight of the container, the wall thickness at the midpoint, IR spectrum, thermal analysis by DSC, light transmission, heavy metals and other tests.

Reference substances

Secondary working standards were qualified against primary reference standards. Working reference substances were also purchased and traced back to primary reference substances.

Reserve samples

The retention samples were stored in the warehouse building under the control of the site QA. This was not inspected due to time constraints.

The deficiencies noted from the good practice in the quality control section have been addressed satisfactorily and the same will be verified during future PQ inspections.

Part 3	**Conclusion – Inspection outcome**

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***, located at ***Block-N2, Village Theda, PO: Lodhi Majra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101 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.

Part 4	**List of WHO Guidelines referenced in the inspection report**

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
https://digicollections.net/medicinedocs/documents/s21467en/s21467en.pdf

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***
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