

WHO PUBLIC INSPECTION REPORT (WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Ipca Laboratories Limited
Unit number	N/A
Production Block	N/A
Physical address	1, Pharma Zone, SEZ Indore, Pithampur 454775, Madhya Pradesh, India
Postal address	As above
Date of inspection	7 - 10 February, 2011
Type of inspection	Routine inspection
Dosage form(s) included in the inspection	Tablets
Summary of the activities performed by the manufacturer	Manufacture, quality control and release of: <ul style="list-style-type: none"> • Tablets - coated and uncoated • Hard gelatin capsules • Pellets in capsules
Scope and type of inspection	Routine GMP inspection
Programme	Prequalification of Medicines Programme

Part 2: Summary

General information about the company and site

Ipca has multi-location facilities in India at:

Piparia. This site FPP facility is approved by US FDA and MHRA UK

- Kandla. This site Penicillin manufacturing facility is approved by MHRA-UK, MCC-SA, TGA-Australia and NDA-Uganda.
- Ratlam. This site has bulk drug plants which are approved by US FDA, EDQM-Europe, TGA-Australia; ANVISA-Brazil, MCC-SA and WHO. The FPP plant is approved by MCC-SA and NDA -Uganda
- Indore
- Athal. This site FPP facility is approved by MHRA-UK, MCC-SA, TGA-Australia and WHO
- Dehradun
- Aurangabad

The Pithampur manufacturing site is located 42 km from Indore. The buildings were 4 years old. Pharmaceuticals Oral Dosage Formulations are manufactured at Ipca Laboratories Limited, Pithampur. The products manufactured at the site comprise Generics and Proprietary Medicines.

The site started manufacture of validation batches for new submissions in 2009.

At the time of the inspection the site employed approximately 211 employees; 103 of which worked in pharmaceutical production activities, 21 in Quality Assurance (QA) and 36 in Quality Control (QC).

History of WHO and/or regulatory agency inspections

The Ipca Pithampur site was not previously inspected by WHO.

The Site was approved by FDA India and was inspected by MHRA UK in October 2010. This site is licensed to manufacture Oral Solid Dosage Forms (Tablets and Capsules) under manufacturing License number 25/1/2008 & 28/1/2008 issued by Food and Drug Administration, Bhopal (Madhya Pradesh), India. The manufacturing license is renewed every 5 years. The current license is valid to 22/01/2013.

Focus of the inspection

The inspection focused on the production and control of prequalified product. 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.

2.1 QUALITY ASSURANCE

A system for quality assurance was established and covered all the basic elements of GMP.



Change Control

A formal system for change control was described in a written procedure and flow chart. A change control register was available. Changes were classified as:

- Major
- Minor

The Change Control (CC) register for 2010 was reviewed. No comments were made by the inspectors.

A change control form was reviewed: no comments were made by the inspectors.

Deviation management

Deviation management was described in a written procedure. A deviation register was available.

Risk Assessment (RA)

A RA SOP explaining the approach to HACCP was available.

Quality management review

SOP as well as Management review report July, 2010 to December, 2010. was reviewed. SOP and report were found to be acceptable.

Product Quality Report (PQR)

SOP Procedure for Product Quality Review (PQR)" was reviewed. According with SOP PQR should be carried out for each product manufactured in the plant.

SOP Out of trends was reviewed; some comments were made by the inspectors.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

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.

Standard operating procedures gave detailed directions to staff and employees on items such as restrictions on smoking, eating, and toilet procedures. This was found to be satisfactory.

SOP "Procedure for Personal Hygiene Practices" was reviewed. Document was available in English and local languages. No comments were made by the inspectors.

Manufacturing and packing areas were cleaned according to approved documented cleaning procedures.

2.4 QUALIFICATION AND VALIDATION

The company's approach to qualification, and validation was consistent with the WHO technical report series recommendations.

Calibration

The company had established a calibration program, which provided calibration effort to be equipment which was used for testing, measuring, or inspection service. Equipment calibration was done at regular intervals. This had satisfactorily been done for equipment such as balances, laboratory equipment and instruments.

Process Validation protocol report for specific product was reviewed by the inspectors.

The batch manufacturing records or specific product were reviewed and were considered to show complete details.

SOP "Procedure for Cleaning Validation" was reviewed. Equipment drawings were available and sampling points were specified. The surface area of equipment was based on engineering drawings supplied by the equipment manufacturer.

2.5. COMPLAINTS

The company approach to dealing with complaints was explained in the SOP. A Complaint register was available and shown to inspectors.

SOP Procedure for handling of product complaint" was reviewed. Quality Assurance personnel were responsible for investigation of complaints. Complaints were classified as:

- Critical
- Major
- Minor

2.6 PRODUCT RECALLS

There had been no recalls up to the date of the inspection.

SOP "Procedure for Product Recall" was reviewed. Recalls were classified as:

- Class I
- Class II
- Class III
- Class IV

If there was no recalls, according with SOP recall effectiveness should be evaluated within 3 years.

2.7. CONTRACT PRODUCTION AND ANALYSIS

SOP "Procedure for selection and approval for Contract Testing Laboratories" was reviewed. Four testing contract laboratories were used if necessary. Contract laboratories have been audited once in a year.

Contract laboratory audit report was reviewed: no comments were made by inspectors.

A number of Technical agreements were reviewed no comments were made by inspectors.

2.8. SELF INSPECTION AND QUALITY AUDIT

The company had a basic self inspection program which consisted of semi-annual reviews of all of its operations, and production activities. There was a standard operating procedure to cover the basic approach to self inspection, and an annexed set of checklists designed to cover different manufacturing activities in different areas.

2.9. PERSONNEL

In general, the personnel met and interviewed during the inspection were confident in what they were doing. Job descriptions of key persons were available and the following were reviewed:

- Production Manager
- Manager QC
- Deputy General Manager - QA
- Manager - QA

2.10 TRAINING

The training needs were identified and training was organized as per SOP "Procedure for training of plant personnel". There were several types of training explained in the SOP.

Training effectiveness was evaluated by the questions and multiple choice or True or False answers.

SOP "Procedure for training and certification of analyst" was reviewed. For the analysts certification "Coded samples" were given to analyst and results were compared against a key. Analyst's re-certification was carried out for all analysts once in two years.

2.11. PERSONAL HYGIENE

Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product. All changing rooms were provided with photographs which described the gowning procedures. Level of personnel hygiene was observed to be appropriate.



2.12. PREMISES

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Premises were designed to ensure the logical flow of materials and personnel. Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Sufficient space was provided for samples, reference standards, solvents and reagents.

2.12. EQUIPMENT

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibrated standard weights used for in-house checking of balances were available. Calibration due-date labels were attached to the equipment.

Daily checking of analytical balances was carried out using 5 different calibrated standard weights; monthly calibration was carried out using 11 weights. Standard weights calibration certificates were presented to inspectors.

Production equipment was cleaned on a scheduled basis. Cleaning check lists were available for all equipment.

Equipment calibration schedule and planned preventive maintenance program (PM) of equipment and systems was in place. Spot checks showed that the schedules had been followed and records were maintained.

SOP "Procedure for preparation of calibration planner and tolerance" was reviewed. SOP was applicable for QCL equipment. Yearly and monthly calibration planners were available.

SOP "Procedure for Preventive Maintenance of plant equipment/system" was reviewed. PM was carried out according with Check list. Check lists were available for all equipment.

HVAC

The HVAC system was well designed and maintained. A separate room was provided for the air filter washing and cleaning. An adequate number of spare filters were stored in a separate room.

Reviewed AHUs Installation Qualification reports were very comprehensive documents.

Re-qualification was carried out every 6 months for all tests following ISO 14644.

The utilities section was visited and a numbers of AHUs were checked. There were no major issues observed.

Purified Water System

SOP "Procedure for Operation of the Purified Water Distribution" and SOP "Procedure for operation of Purified water distribution loop" were reviewed.

Welding records were available. Pipelines were connected by using orbital welding. Print outs of orbital welding machine were available and presented to the inspectors. Boroscopic welding was recorded on CD.

2.14. MATERIALS

Materials were properly quarantined and released by QC. Temperature was controlled. Temperature mapping was carried out; reports were presented to the inspectors.

Printed packaging materials were stored in a locked area.

Materials were received via two unloading platforms; proper checks according to the check list were carried out for incoming materials. Approved vendors list was available in the warehouse. All incoming materials were de-dusted before placing to the quarantine area.

100% sampling plan was applied for API sampling for identity tests.

Printed packaging materials were sampled following AQL, inspection level II. Defects - critical, major and others were specified.

There were two sampling and two dispensing rooms which had separate personnel and material entrances. Sampling and dispensing was carried out under the RLAF

There was one sampling/dispensing room dedicated for the packaging materials sampling and dispensing. Sampling and dispensing was carried out under RLAF.

Rejected materials were stored in locked room.

Finished goods were stored properly.

2.15. DOCUMENTATION

In general, the documentation system was established and maintained. Documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. A system for version control was in place. Specifications and testing procedures were available. Documents related to the batch release were stored one year after the expiry date of the batch.

2.16. GOOD PRACTICES IN PRODUCTION

Handling of materials and products was done in accordance with written procedures and was recorded. Temperature and relative humidity in the production rooms were continuously monitored.



The general design of the facilities was appropriate. Maintenance of the premises was good.

The manufacturing activities were organized in a logical stepwise manner; processes were completed in accordance with authorized batch manufacturing records, similarly, the Packaging effort was conducted in accordance with authorized Batch Packaging Records.

Punches were stored properly, were numbered and rotation was ensured. Food grade lubricant was used for punches and dies lubrication. Finger bags were product dedicated.

During the inspection the only production activity which was carried out was compression of tablets in the compression cubicle unrelated to the product under review, and a granulation step of another product.

Cleaned equipment hold time studies were carried out.

2.17. GOOD PRACTICES IN QUALITY CONTROL

The laboratory was well designed and adequately equipped. It was noted that not enough space was provided in the instrumental laboratory to carry out samples preparation and data recording.

Reference substances

SOP "Procedure for procurement preparation, qualification and handling of analytical standards" was reviewed. Working standards (WS) were dispensed in vials (2-5g) for monthly use. Usage of standards was recorded. WS were dispensed in un-controlled environment. Standards were stored properly.

Stability studies

SOP "Procedure for stability study of drug product", stability study protocol and stability schedule were reviewed. No comments were made by the inspectors. Stability schedule was followed. Two months accelerated stability study results and raw data was presented to the inspectors. All results were well within the limits.

Microbiological laboratory (MBL) was well equipped and maintained.

The Media preparation SOP was available. A Growth promotion test using both culture collection micro-organisms and in house isolates was carried out for each batch of dry media and each lot of sterilized media. Positive and negative controls were carried out.

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, a decision on the compliance of Ipca Laboratories Limited, located

at 1, Pharma Zone, SEZ Indore, Pithampur 454775, Madhya Pradesh, 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.