

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Ranbaxy Laboratories Ltd
Physical address	Paonta Sahib, District Sirmour Himachal Pradesh India 173 025
Postal address	Village Ganguwala, Paonta Sahib, Dist Sirmour, Himachal Pradesh India
Telephone number	+91-1704-222834
Fax number	+91-1704- 223492
Summary of all the activities performed by the manufacturer (e.g. manufacturing, packing). Indicate dosage forms and type of products (e.g. tablets; penicillin or cephalosporin containing products)	Manufacturer and packer of oral solid dosage forms Tablets, HGC and SGC
Scope of inspection	General and Product Specific GMP inspection with data verification. Block F and limited aspects of other blocks Pharmaceutical dosage forms: Tablet and capsule manufacturing (HGC)
Date of inspection	November 23-25, 2009
Programme	Prequalification of Medicines Programme

Part 2: Summary

The manufacturing site of Ranbaxy Laboratories Ltd, India, (hereafter referred to as Ranbaxy) which was located in Paonta Sahib, India, was inspected by a WHO prequalification inspection team on the above mentioned days.

General information about the company and the site, History of WHO or regulatory agencies inspections

Ranbaxy has manufacturing units in 8 countries: 6 API manufacturing units in India, 6 dosage forms manufacturing units in India and 13 sites overseas. FPP's and API (fermentation) were manufactured at the Paonta site however Betalactam and/or Cephalosporin products were not manufactured here.

The Paonta Sahib site was located around 125 km from Chandigarh and 260 km from Delhi.

Pre-qualified products were currently manufactured in Blocks A and C along with numerous other regular pharmaceutical products. Company was planning to manufacture WHO approved products also in Block F, this inspection specifically covered the activities in Block F. The company was planning to submit the variations for this change to WHO in the near future.

In total there were approximately 587 employees working at the site of which 143 were involved in QA/QC activities.

Focus of the inspection

The focus of this inspection was to verify production and quality control activities and to assess compliance with WHO GMP. Only production Block F was inspected, as the company were planning to submit variations for product transfer to block F.

2.1. Quality Assurance (QA)

A quality assurance system was implemented and maintained

The QA unit and QC units were independent from production with the Head of Quality Unit reported to the Vice President Global Quality. The Head of Quality Unit was also the Authorized person and the second authorized person was the General Manager QC.

Change controls covered all changes including documentation, processes and equipment and were defined in SOP. The impact of change was assessed by appropriate departments and the minimum number of department reviews was defined. There was also an implementation checklist which defined the documents which had to be approved. Various change controls were reviewed.

A compression machine equivalency report was reviewed as part of change control and this covered various factors such as operating principle, operating principle, feed type,

number of stations, rpm, dwell time and pre-compression. The evaluation was conducted in an appropriate manner and gave confidence that the product would be manufactured appropriately if it is transferred to another machine.

Deviations were classified into three categories, critical, major and minor.

Trending of deviations was carried out but these did not provide much information. The company were working to improve this through the use of consultants PRTM.

A number of annual product review (APR) was reviewed.

The APR was prepared in accordance with the revised SOP.

A quality risk management procedure had been implemented. Risk assessment and management protocol was available and was applicable to facilities, processing and product quality. In 2009 three products, based on the criticality of manufacturing process, sensitivity of drug product and the longest manufacturing process were selected to undergo this review. The Review considered if critical control points and HACCP was used as the assessment tool. Reviews were done by QA senior manager and production manager during the production of batches and the company was planning to perform such reviews annually, however this was not specified in the SOP.

2.2. Good manufacturing Practices for Pharmaceutical products

Good manufacturing practices were implemented and generally maintained.

The manufacturing steps were recorded in the Batch Manufacturing Records (BMR) and records were made during manufacture.

Instructions and procedures were generally written in clear and unambiguous language.

2.3 Sanitation and Hygiene

The topic was not specifically covered during the inspection; however no notable concerns were identified during the inspection. The hygiene measures in place at the time of the inspection were generally found to be sufficient to assure the prevention of contamination of the premises and product.

2.4 Qualification and Validation

The key elements of the qualification and validation program were defined and documented in the Validation Master Plan.

Cleaning validation was performed in accordance with SOP and a computer system had been developed to store this data.

The approach taken for the cleaning validation was to identify the product with the least solubility and validate this product as the worse case.

The protocol/report for revalidation of the cleaning process for specific product was reviewed:

The surface area of the equipment and equipment trains were inserted into a formula from cleaning validation literature to determine the acceptance criteria for this product which was determined as less than 20µg. The surface area raw data calculation for the specific equipment were reviewed and found to be acceptable.

"Analytical method validation protocol for specific product in swab samples" was reviewed. The swab recovery limit was set as NLT 80 % and precision, lack of interference from excipients and swabs, linearity, sample robustness, LOD, LOQ were determined to be satisfactory.

A number of documents were reviewed and found to be acceptable.

Cleaning effectiveness was monitored periodically for:

- Operator variability
- Equipment aging & repair
- Changes to the product, equipment, process of batch size

Periodic re-qualification was conducted annually in accordance with "Monitoring schedule of equipment cleaning process efficacy" on equipment which was randomly selected.

Process validation

The prospective validation protocol/report for specific product was reviewed.

The V blender was used for the original validation studies but was not available in Block F, however equivalent equipment for blending and tablet compression was available in Block F and used for manufacture. The certificate of equivalence of tablet compression machine and Equipment Equivalency protocol for tablet compression machines as well as Certificate of equivalence of V blenders and Equipment Equivalency protocol for V blender were therefore reviewed and found to be acceptable.

The process validation report for specific product was also reviewed and the results indicated low RSD results indicating good reproducibility.

2.5. Complaints

Complaints and other information concerning potentially defective products were reviewed according with SOP.

Complaints were classified as Critical, Major and Minor/others and were recorded in the complaint log books and market complaint lists. A new SOP for market complaints and a new log book was implemented recently.

CAPA's were generated for all critical and major complaints in accordance with written SOP. The complaint investigation was completed within 30 days and if necessary a decision about recall was considered in accordance with SOP.

A number of complaints in 2008 and in 2009 up to the date of inspection were reviewed.

The investigation report on market complaint for specific product and Trends analysis of market complaints and market complaint analysis for the year 2008 were reviewed.

2.6 Product Recalls

Recalls were handled in accordance with a written SOP. The recall classification was: Class I, class II and class III and the time limit for the initiation of a Class I and II recall was specified as 3 business days.

2.7 Contract production and analysis

Manufacturing activities were not contracted out although five contract laboratories were used for some analytical testing. Contract workers were also used for the cleaning of the production facilities.

2.8 Self inspection and Quality Audits

This area was not covered during this inspection.

2.9 Personnel

The personnel met during the audit were experienced, skilled and conscientious.

2.10 Training

The training files for QC department staff were reviewed. Induction training was carried out on recruitment and this was confirmed for these analysts. Every six months the analysts were given a sample of known potency and they must obtain the correct result.

2.11 Personal Hygiene

The topic was not specifically covered during the inspection but no notable concerns were identified during the inspection of the production areas and the level of hygiene observed was considered satisfactory. All changing rooms were provided with photographs which described the gowning procedures.

2.12 Premises

The buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance, and production operations. The production areas had adequate space around equipment and good material flow to prevent mix-ups and contamination with separate personnel and material entrances.

Storage areas

The receiving and dispatch areas had protection of materials and products from adverse weather conditions.

There were two main materials warehouses. Materials in the warehouses were stored in good order and rejected materials were stored separately and securely. Each block also has its own warehouse operating to the same quality standard.

Production areas

Block F was divided into 3 zones where blending, granulation, compression and coating were carried out. The packing area was small and consisted of two segregated lines for bottling and blister packing.

Quality control (QC) areas

The Quality Control Laboratory (QCL) had moved to a new location which was separated from the production building which was previously used by R&D. Adequate space was provided for the storage of samples, laboratory reagents and reference standards, solvents, reagents and records.

2.13 Equipment

Process equipment was installed and maintained in a manner that minimized the risk of error and contamination. Calibrations due date labels were attached to the equipment and the last calibration of a Mettler Toledo balance was reviewed and found to be satisfactory.

QCL equipment

QCL laboratory equipment was moved to the new laboratory block and re-qualification protocols/reports were available following this move.

2.14 Materials

Material management was done by the SAP system which was modified after the last inspection for API vendors and manufacturing sites. Manufacturing sites and vendors were both linked to the material code which was approved by QA.

Material receipt

All incoming materials were received at the central warehouse. Materials were quarantined until tested and released by QA with separate locations for materials under quarantine and approval and for rejected materials. Materials were checked appropriately on receipt and there was segregation of quarantined and released materials. An approved vendor list for starting materials and packaging materials was available in the warehouse.

NIR

NIR was used to confirm the identity of some materials on receipt and the validation of the library for specific product was reviewed where data was presented to confirm precision, selectivity, reproducibility. The system was secure with regular password changes. Composite samples were tested as per the Standard Tests Procedure.

Storage conditions

Materials and products were stored in a proper manner.

Controlled temperature storage

For controlled areas temperature, the limits were 15 -25 °C with RH at 40-65%.

API's were stored in a controlled temperature room. Aluminum foil and capsules were also stored in a controlled environment. Temperature was continuously controlled by data loggers in defined locations. Temperature mapping in the warehouse had been carried out. Two permanent monitoring positions were then selected based on the worse case results for high and low temperatures.

The company were looking to air condition the whole warehouse in the future.

Dispensing

Separate dispensing booths were provided for excipient dispensing , API dispensing and liquids dispensing.

Dispensing was carried out using a new dispensing system linked to SAP since September 2009. The identity of the container was confirmed using a bar code scanner. Checks confirmed that the system ensures that the check-weighing of balances before use, and that cleaning was carried out before allowing the dispensing to proceed to the next stage.

Security screening was also attached to the warehouse and documented in the BMR.

There was separate packaging materials quality control laboratory located above the central warehouse.

Packing component sampling and testing

Packaging components were tested on the first floor and the packaging specification for specific product were reviewed and the signatures of the approving marketing or regulatory manager confirmed. Primary packaging materials were sampled under RLAf and capsules were sampled in the excipient sampling room.

Reprocessing operations were defined as: re-drying, re-sieving or milling. Accelerated stability for 3 months was carried after reprocessing and if satisfactory the batch was released.

Reworking was defined as: blending, drying, opening the secondary/tertiary pack and repacking them in different orientation. Accelerated stability study was carried out for 3 months and if satisfactory the batch was released.

2.15 Documentation

In general the documentation system was established and maintained, documents were approved, signed and dated by the appropriate responsible persons, regularly reviewed and kept up to date.

The batch record for specific product was reviewed and found to be satisfactory.

2.16 Good practices in production

Production operations were performed following defined procedures and line clearance was performed and recorded before processing operations were started.

Block F production facilities were inspected in detail. The general design of the facility was appropriate and it was maintained on a regular basis. Some damage to walls was seen in some areas.

General processes were under good control and blending, granulation, compression, capsule filling and coating areas were visited. The wash area had good flow of dirty and clean equipment and nylon brushes were discarded after use. Filter bags were dedicated for each product. There was a central IPQC room containing the usual equipment for controlling compression parameters where the calibration of the tablet hardness machine was reviewed.

A number of production SOP's were reviewed.

The following were also confirmed:

- Metal detectors were challenged at the beginning and end of the shift using ferrous, non-ferrous and stainless steel probes.
- Dedicated finger bags were used for the each product and stored in locked cabinets.
- Punches and dies were properly stored and maintained. Turn over of punches and dies was measured and recorded in the tablet tooling log card.
- QA approved lubricant was used for the punches and dies storage.

Technology Transfer

The technology transfer process was reviewed for specific product and was considered comprehensive and covered batch formula, storage, test methods and stability. It also included a product development report, an impact assessment on cleaning validation and a method transfer for the analytical test methods.

Environmental monitoring

There was an environmental monitoring programme in place based on the requirements in SOP which requires settle plate and contact plate monitoring for bacteria and fungi of all the production facilities. The results were satisfactory and were within the defined limits when the trend for 2008 and actual results for 2009 were reviewed.

2.17 Good practice in Quality Control

In general Good Practice in Quality Control was implemented and maintained and there was adequate facilities, trained personnel and approved procedures available. Records of analysis were 100% checked by QA staff and the C of A was signed by the technician who performed analysis, checked by the supervisor and approved by the QA manager.

OOS

OOS results were evaluated and investigated in accordance with SOP. This SOP was not applicable to microbiological laboratory testing, packaging materials testing or Out of Trend review.

The number of OOS were recorded and reviewed.

Microbiological testing OOS results were evaluated and investigated in accordance with SOP. There was no OOS reported till the date of inspection.

Out of Trend results were evaluated and investigated in accordance with SOP.

The number of OOT reports were reviewed.

All QC equipment was re-qualified when it was moved to the new QC building which was formerly a development facility for fermentation and HPLC were linked to the Empower data management system.

HPLC maintenance was carried out by the manufacturer of the systems which was followed by calibration by internal personnel every 6 months. The calibration of specific HPLC was reviewed and the expected checks on injection accuracy, precision, linearity, etc. were carried out.

Analytical data was checked as per SOP and there was a detailed checklist for review and spreadsheets for checking data were confirmed as being protected.

Primary reference and working standards (WS) were properly stored. Working standards (WS) were dispensed under the LAF and were transferred once per year to 24 amber glass bottles following qualified against primary reference standards in accordance with SOP After opening, the bottle was used for 15 days.

Specific API WS preparation and qualification records were evaluated and found to be acceptable as the analysis was performed in triplicate.

Usage of primary reference and WS was recorded; the standards usage log books were available for inspection.

Dry chemicals and solutions expiry dates were set 5 years after date of receipt or 2 year after opening the bottle of dry chemical or 3 months after opening the bottle for solutions and all volumetric solutions and reagents were properly labeled.

HPLC columns were dedicated for the product and properly stored in the cabinets. Each column had a usage log book and specific column usage log book was reviewed. C of A were available for the columns and the discard of the columns were recorded. Purified Water used for HPLC tests was checked for pH and conductivity daily and recorded in

the log book. The mobile phase expiry date was set at 7 days and HPLC vials were re-used and washed manually.

Dissolution apparatus calibration was performed by the technicians. Physical parameters such as RPM, temperature, wobble and centering of paddles were calibrated every three months and system suitability tests were performed once per six months using USP Prednisolone and acetylsalicylic acid tablets were used.

Retention samples were properly stored and maintained in three samples storage rooms which were temperature mapped which were monitored continuously by five on-line data loggers in the each room. Additionally there was stand alone minimum - maximum temperature recording equipment.

Microbiology

The laboratory conducted water, raw material, finished product and stability testing. The preparation of media was investigated and growth promotion testing which appeared to be satisfactory. There was a separate autoclave for media sterilisation and for destruction. Thermocouple testing was carried out by an external party and the results were satisfactory.

Stability studies

The stability data for specific product which were packed in HDPE bottles containing 60 tablets for Africa was reviewed. The results up to the 18 month time point were all within specification.

Utilities

HVAC system

The inspection of the air handling system entailed a visual inspection of the equipment in the plant room, checks against drawings and re-qualification which was contracted out.

During inspection attention was focused on two AHU.

EU4 - EU7 - EU9 filters were installed in the plenum. Terminal HEPA-EU12 filters were installed in production rooms and air was re-circulated.

Periodic revalidation of HVAC systems / UAF systems and HEPA filters were performed in accordance with protocol and the following tests were performed:

- Airborne particle count - once per year
- Air flow test (feet³/min) - once per year
 - Air velocity feet³/min
 - Air changes per hour
- Air pressured difference test - once per year
- Installed filter leakage test - once per year
- Air flow visualization test - once per 2 years
- Temperature - once per year
- RH - once per year

- Recovery test - once per 2 years
- Containment test - 1 per 2 years

Purified water system

The Purified Water (PW) system for Block F was inspected. The Christ Osmotron system appeared to be well maintained. PW was produced by RO and EDI and associated pretreatment by softeners and filtration. PW was continuously circulated at ambient temperature which was controlled by a flow meter and jacketed cooling of the main tank. Conductivity was controlled on line at two points after the PW storage tank and after the recirculation loop on return to the tank and water was automatically dumped to drain if limits were exceeded. UV lamp working hours and intensity was controlled continuously. The system was sanitized weekly by heating and sanitization and maintenance was recorded. Recirculation of the PW was through PVDF pipe work which was FDA approved and the certificate of conformity (PVDF) for PW system distribution lines was reviewed.

Part 3: Conclusion

Based on the facilities inspected, the personnel met and the documents reviewed, and considering the inspection observations listed in the inspection report, Ranbaxy Laboratories India located in Paonta Sahib, India, were considered to be operating at an acceptable level of compliance with WHO GMP.

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.