



**WHO PUBLIC INSPECTION REPORT**

**(WHOPIR)**

**Finished Product Manufacturer**

**Part 1: General information**

Name of Manufacturer	Ranbaxy Laboratories Limited
Unit number	Unit I & II
Production Block	N/A
Physical address	Village Ganguwala, Paonta Sahib, Himachal Pradesh, India
Contact address	Same as above
Date of inspection	18 - 21 April 2011
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Tablets and capsules
WHO product categories covered by the inspection	HA286 HA290 HA294 HA296 HA297 HA298 HA299 HA300 HA301 HA302 HA305 HA306 HA322 HA323 HA324
Summary of the activities performed by the manufacturer	Manufacture and control of pharmaceutical products manufactured in Block C

## **Part 2: Summary**

### ***General information about the company and site***

Ranbaxy Laboratories Limited (hereafter RLL) has its head office located in Gurgaon, Haryana, India. The company has five API manufacturing facilities in India and seventeen formulations units in India and abroad. RLL Paonta Sahib Plant is located at Paonta Sahib, District Sirmour, Himachal Pradesh, India. The facility includes raw materials and packaging materials warehouse, dedicated and segregated areas for the manufacture of tablets and capsules (hard & soft gelatin).

The site has a pilot plant for carrying out development trials on fermentation based APIs and also manufacturing unit for the same. The site also has a process development laboratory for the manufacture of scale up and test batches and a separate stability cell for conducting stability studies. In addition, the site also has a separate manufacturing facility for the manufacturing of food grade soft gelatine capsules.

### ***History of WHO and/or regulatory agency inspections***

The last inspection of this site by WHO was in November 2009.

Following changes were made/proposed after the last inspection:

- Mr AK Sharma joined as Head Pharma Manufacturing (Plant Head)
- Mr Sunil Singh joined as General Manager - QA (head - QA)
- Exhibit stability department has been made part of plant quality unit. The exhibit stability department was earlier part of the analytical research and development. Now, the exhibit stability head is Dr Vipin Kumar who reports to Site Quality Head.
- Equipment such as blender, coating pan, RMG, cage lifter, blister packing line, roller compactor etc installed in block F; and some changes were made in equipment in block A, C and D.
- Warehouse receiving bay ramp extended
- Each production block monitored by IPQA managers.

### ***Focus of the inspection***

The inspection focused on the production and control of some of the pre-qualified products. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.



***Inspected Areas***

<b>Day 1</b>		
Morning	<p><b>Opening meeting</b></p> <ul style="list-style-type: none"> <li>• Introductions</li> <li>• Attendance Record</li> <li>• Confirmation of scope of inspection and inspection plan</li> <li>• Company overview and presentation (about 15 minutes)</li> <li>• Summary of manufacturing processes and product range</li> <li>• Changes since last inspection and proposed changes.</li> </ul>	
	<p><b>Personnel</b></p> <ul style="list-style-type: none"> <li>• Organization Chart</li> <li>• Job descriptions for key personnel</li> <li>• Training procedures and records</li> </ul>	
Afternoon	<p><b>Quality Management</b></p> <ul style="list-style-type: none"> <li>• Product Quality Review</li> <li>• Quality Risk Management</li> <li>• Complaints</li> <li>• Recalls</li> <li>• Deviation control</li> <li>• Change control</li> <li>• Contract agreements</li> <li>• Supplier approval</li> <li>• Document Control</li> <li>• Self inspection</li> </ul>	

<b>Day 2</b>		
Morning	<p><b><u>Site inspection</u></b></p> <p><b>Buildings and Facilities</b></p> <ul style="list-style-type: none"> <li>• Design and construction</li> <li>• Layout of site, HVAC, Water systems</li> <li>• Personnel and material flow</li> </ul> <p><b>Warehouse(s)</b></p> <ul style="list-style-type: none"> <li>• Storage – quarantine, release, reject</li> <li>• Materials</li> <li>• Receipt, handling and storage</li> <li>• Identification</li> <li>• Sampling</li> <li>• Status Control</li> <li>• Weighing/dispensing/issuing</li> <li>• Temperature (and humidity) monitoring</li> <li>• Packaging materials</li> <li>• Finished Products and distribution</li> </ul>	
Afternoon	<p><b>Production</b></p> <ul style="list-style-type: none"> <li>• Batch document preparation</li> <li>• Production area</li> <li>• Packaging</li> </ul>	



	<ul style="list-style-type: none"> <li>• Cleaning</li> <li>• Finished product release</li> <li>• Batch record review</li> </ul>	
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<b>Day 3</b>		
Morning	<p><b>Inspection of Production - continued</b></p> <p><b>Engineering &amp; Services and utilities such as HVAC and water:</b></p> <ul style="list-style-type: none"> <li>• Preventive Maintenance</li> <li>• Calibration</li> </ul>	
Afternoon	<p><b>Inspection of Quality Control Laboratory</b></p> <p><u>Organization and management</u></p> <ul style="list-style-type: none"> <li>• Quality management system</li> <li>• Personnel, training and assessment</li> <li>• Premises</li> <li>• Sampling and sample handling</li> <li>• Work allocation</li> </ul> <p><u>Documentation</u></p> <ul style="list-style-type: none"> <li>• Specifications and test methods</li> <li>• SOPs, logbooks, records</li> <li>• Worksheets and test reports</li> <li>• Contract testing, Stability program</li> <li>• OOS results, Analytical method validation</li> <li>• Evaluation of results, release and rejection procedures, Trending of results, Traceability</li> </ul> <p><u>Materials</u></p> <ul style="list-style-type: none"> <li>• Chemicals and reagents, Reference standards</li> <li>• Retention samples</li> </ul> <p><u>Equipment, instruments and devices</u></p> <ul style="list-style-type: none"> <li>• Operation and maintenance</li> <li>• Calibration and qualification</li> </ul> <p><u>Microbiology</u></p> <ul style="list-style-type: none"> <li>• Personnel</li> <li>• Premises, environment</li> <li>• Equipment</li> <li>• Reagents and culture media, preparation and control</li> <li>• Reference materials and reference cultures</li> <li>• Sample handling</li> <li>• Purified Water monitoring</li> <li>• Environmental monitoring</li> <li>• Testing of materials and finished product</li> <li>• Disposal of waste</li> <li>• Dissolution data including comparative dissolution</li> </ul>	



<b>Day 4</b>		
Morning	<p><b><u>Inspection of Utilities / QC continued</u></b></p> <p><b><u>Documentation review</u></b></p> <p><b>Validation and qualification:</b></p> <ul style="list-style-type: none"> <li>• Validation Master Plan</li> <li>• Validation and qualification status (matrix) and schedule</li> <li>• Equipment qualification</li> <li>• Process validation</li> <li>• Cleaning validation</li> <li>• Computer validation</li> </ul>	
Afternoon	Summary by inspectors (closed meeting)	
	Closing meeting with company representatives	
	End of inspection	

## 2.1 QUALITY ASSURANCE

In general, the quality assurance system was found appropriate to the manufacture of pharmaceutical products. The production and control operations were clearly specified. However, managerial responsibilities were not clearly specified in job descriptions. In particular, job descriptions of Head Pharma Manufacturing and Senior Manager Warehouse didn't cover the tasks assigned to them. Similarly, the job description of head quality and/or his designee didn't state responsibility for the release of pharmaceutical products.

In general, an adequately designed and correctly implemented system of quality assurance was in place with competent personnel and facilities.

## 2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general, manufacturing processes were defined and reviewed adequately to ensure pharmaceutical products were manufactured consistently with required quality.

During the inspection, it was noted that Ketoprofen tablets 100mg was under drying in the FBD. There were some discrepancies noted on the drying time specification versus actual drying time used before compression. For more detail, refer observation.

Equipment and instruments were qualified before use and manufacturing processes were validated.

Operators interviewed during the inspection were found competent and trained to carry out the tasks assigned to them.



The SOP on product quality review was reviewed. However, the SOP didn't describe acceptance criteria for CpK to ensure processes were robust and consistent.

The PQR report for Abacavir Sulfate Tablets 300mg was reviewed. There were some issues noted pertaining to the type of tests reviewed for Abacavir Sulfate Tablets and their Cpk results.

The documents on risk assessment and management and risk assessment and classification were reviewed. In general, these documents appeared adequate except that there were some discrepancies noted on the criteria set for critical risk versus examples given in the document.

### **2.3 SANITATION AND HYGIENE**

A general approach and procedures were in place to ensure that an acceptable level of cleanliness was achieved. The level of sanitation and hygiene within the facilities was acceptable. Thorough gowning procedures were in place.

The SOP on Pest Control, Rodent Control, Fly Control & Insect control was reviewed and found satisfactory. However, lay out of the bait station was not clear and didn't clearly identify the exact location of glue mates in receiving bay and warehouse area.

### **2.4 QUALIFICATION AND VALIDATION**

RLL identified qualification and validation of equipment and manufacturing processes respectively to ensure critical operations were controlled. Revalidation calendar 2011 was reviewed and appeared satisfactory.

The process validation report (May 2010) of Efavirenz coated Tablets 600mg was reviewed during the inspection. The batch size was 480.0kg (equivalent to 400,000 tablets) and three batches were taken for process validation. These batches were first prepared in two lots and eventually mixed and further blended in V-shaped blender. Critical process parameters were checked by taking samples after blending and after compression of tablets (start, middle & end of compression stage). Relative standard deviation for the blend uniformity samples found less or equal to 1% in all three batches. The final coating weight build up was within 1.5 to 2.0%. Yield was also found within the anticipated limit (93-100%).

The validation master plan effective date 1/8/2009 was reviewed and found satisfactory in general. The VMP described the approach for qualification, supplementary qualification, re-qualification, re-validation, equipment equivalence for area/room qualification, HVAC system, dust control system, water system, compressed air, nitrogen gas, common utilities, process validation, cleaning validation, analytical method validation, computer system and deviations.

The procedure to perform cleaning validation study effective date 16/4/2011 was reviewed. It was noted that cleaning validation was carried out using solubility (practically insoluble), therapeutic drug level, and highest strength criteria. The document appeared satisfactory.

### **2.5 COMPLAINTS**

The system in use for handling complaints was acceptable. The procedure for handling market complaints effective date 10/5/2010 and its associated logs were reviewed. It was noted that



classification of complaints into critical, major and minor was not based on the risk associated to patient. Moreover, complaint serial number denoting various regions was not defined in the SOP and no time limit was specified for the prompt handling of critical and major complaints. SOP on defining region was available; however it was not cross referenced to the SOP on complaints.

2009: In 2009, altogether 253 complaints were received and mainly related to Isotretinoin capsules. There was no trending done on complaints received in 2009.

2010: It was found that 232 complaints were received in 2010. Out of which, 95 complaints were classified as major and rest were classified as minor (no critical complaint noted in 2010). 95 major complaints were further classified into shop floor related complaint, medical, storage/handling and pack related complaints. Trending on complaints for 2010 was available and reviewed.

A discrepancy was noted on a complaint for Efavirenz 200mg capsule regarding its batch number and inappropriate follow-up action. For more detail, refer observation.

A person responsible for the handling of complaints and recalls was interviewed and found to be competent in the task assigned.

## **2.6 PRODUCT RECALLS**

SOP on product recall procedure and its associated logs were reviewed and found adequate in general.

2009: Isotretinoin Capsules 40mg failed in dissolution. It was a voluntary recall based on the fact that product was passed in RLL but didn't comply with specification in third party laboratory.

2010: There were 4 recalls in 2010: Ranitidine HCl tablets 300mg (from Portugal), Perindropil tablet 4mg (Brazil), Ran-Ramipril capsules 1.25mg (Canada) and Provastatin tablets 10 mg & 40mg (UK). Most of these recalls were voluntary in nature as claimed by RLL, Paonta Sahib.

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

It was noted that production activities were not contracted out.

SOP on contract agreement with analytical testing lab was reviewed. There were some issues noted in the SOP as well as in the contract signed between RLL, Paonta Sahib and contract acceptor.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

SOP on self inspection effective date 21/2/2011 was reviewed and found satisfactory.

Annual schedule for self inspection and report on the last self inspection conducted in Jan 2011 were available for review.



## **2.9 PERSONNEL**

Several members of personnel were interviewed during the inspection. They were knowledgeable and experienced. A procedure and plan for training existed.

It was noted that quite a number of staff had joined the organization since last few months or less than year ago. Also, some of the key positions were vacant for some time. There was no specific reason provided by the site management on high turnover rates at the site as well as at the corporate level.

## **2.10 TRAINING**

SOP on training effective date 15/3/2011 was reviewed. It was noted that a new initiative was implemented in 2011 on training using the Learning Management System. Training of a production supervisor was reviewed for the 2010 and found acceptable. There was some ambiguity noted on the retention of training records of employees.

## **2.11 PERSONAL HYGIENE**

During the tour through the facilities no specific observations concerning this topic were made. Gowning and de-gowning procedures were in place and were being followed. In some instances, pictorial presentation on gowning and de-gowning were not available, e.g. sampling and microbiology lab.

## **2.12 PREMISES**

The design, layout, construction and finishing of the facility was in general acceptable. The site was in general maintained at an appropriate level of cleanliness.

The overall site has a number of manufacturing buildings / blocks. Block C building was of an adequate design and construction. A number of improvements have been made to the receiving area since the last inspection.

The warehouse and sampling area were also of an adequate design and maintenance. Additionally more space was under construction for further expansion.

Company had a different air handling system for each areas to avoid the cross contamination. The system was re-circulated with maximum of 10% fresh air and 90% used/re-circulated air but filtered with G4.

## **2.13 EQUIPMENT**

The qualification of some equipment used in Block C was inspected. Generally qualification of equipment was performed in a satisfactory manner. Equipment was qualified before their usage. Also, all equipment and instruments were identified clearly with unique number and calibrated appropriately in the manufacturing, laboratory and warehouse.



## **2.14 MATERIALS**

Rejected starting materials and printed packaging materials were adequately, separately stored. Storage areas were adequately temperature controlled and records seen were satisfactory.

It was noted that there was no temperature monitoring performed in the starting materials receiving area.

Materials were purchased from the approved vendors and a list of approved suppliers was available. Materials were segregated appropriately based on their status and stored appropriately in various areas.

## **2.15 DOCUMENTATION**

Most of the procedures seen during the inspection gave generally sufficient detail on the respective activities performed. The company had a documentation system that covered SOPs, protocols, specifications, reports and records.

In many instances, it was noted that documents were not adequately controlled to minimize confusion. Nonetheless, it was mentioned by the site management that Document Compliance Manager (DCM) system was implemented from Jan 2010 and this might have caused confusion and miscommunication.

The site master file (SMF) was not appropriately prepared to provide accurate information about the site including the responsibilities of the key site personnel, job descriptions, site lay out and equipment etc.

## **2.16 GOOD PRACTICES IN PRODUCTION**

The manufacturing processes were reviewed during the inspection in relation to some of the dossiers submitted to, or pre-qualified by WHO. Activities seen during the inspection were performed in a suitable manner except that in sifting areas, dust extractors were not switched on during the sifting process. Also, it was not known about the containment and pressure cascade when these dust extractors were switched off. For more detail, please refer to observation.

During the inspection, it was noted that return air grille in room PCF 18-IV was not properly installed. However, operation was going on as usual without any action taken or proposed. It is recommended to ensure the appropriateness of the area, equipment and facilities before being used. Nonetheless, inspection team acknowledged the prompt action taken to fix the problem.

With regards to the handling of intermediate and bulk products, it was noted that bulk products were stored next to the return air grill due to the space constraint. It is recommended to adequately store these intermediates without compromising with airflow.

Similarly, in the Fabrication room III, V-shaped blender was placed in addition to FBD and RMG. It is recommended to carry out various processing steps (granulation, blending, drying, compression etc) in their designated /identified areas/rooms. This will enable movement of the personnel and materials logical and would not compromise with appropriate cleaning.



In the Fabrication room I, it was found that there were four dust extractors installed but only two of them were used.

## **2.17 GOOD PRACTICES IN QUALITY CONTROL**

The QC laboratory was inspected, focusing on the activities related to the testing of the materials and products mentioned above.

The manufacturer had procedures and systems in place to ensure that good practices in quality control could be followed. However, there were some issues noted during the inspection of quality control laboratory. For more detail, please refer observation.

The stability chambers were inspected and activities performed with respect to this area were generally satisfactory. It was recommended to review the testing window period for the samples kept for accelerated studies.

### **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, as well as the corrective actions taken and planned, *Ranbaxy Laboratories Limited, Paonta Sahib, 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.