World Health Organization

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WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information

Name of Manufacturer	Cipla Limited
Unit number	Bangalore
Production Block	API-I, API-III, Synthetics-VII and Finishing and packaging block Note: Block numbers changed since last inspection.
Physical address	Virgonagar, Old Madras Road, Bangalore 560 049, Karnataka, INDIA
Contact person and email address.	Mr. Davinder Singh Technical Director Cipla Ltd Mumbai Central, Mumbai 400008, India Email: Davinder Singh dsingh@cipla.com
Date of inspection	18 to 21 March 2014
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Ritonavir APIMF 215 Levofloxacin hemihydrate APIMF 088 Vinblastine Sulfate APIMF 156
Summary of the activities performed by the manufacturer	Production, quality control of APIs.

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Part 2: Summary

General information about the company and site

Cipla Bangalore is part of Cipla Limited, a public Limited Company established in 1935 with the registered office in Mumbai. Cipla Bangalore was established in 1972. It is located 45km from Bangalore airport on a 671,259m^2 plot with a built up area of 39,073.61m^2. Approximately 614 staff are employed at the site with 238 in production, 107 in QC and 33 in QA. The site operates 3 shifts; 7am to 3pm, 3pm to 11pm and 11pm to 7am.

Cipla Bangalore manufactures a range of APIs, but no betalactams, steroids or hormones. A limited range of formulations (tablets and capsules) are also manufactured at this site, but these are in the process of being transferred to another site. The site had nine blocks for the manufacture of APIs and intermediates. The API facilities included multiproduct blocks and blocks dedicated for antineoplastics (synthesis, purification and finishing). The finishing and packaging of non-antineoplastic APIs was conducted in a separate facility on the ground floor of the building for formulations. It was noted that the manufacture of antineoplastics is shortly to be transferred to another site that specializes in this category of API. The company was aware of the need to submit a variation to WHO PQP for this change.

History of WHO and/or regulatory agency inspections

The site was licensed by the Food and Drugs Administration, Karnataka State under licence Nos. NB-110/78 and SP-72/80. This was the 3rd inspection conducted by WHO PQP; the first being in June 2005 and second in June 2011. The site had also been inspected and approved by the MHRA (April 2013), USFDA (June 2012), KFDA (February 2010) and TGA/EDQM (June 2009).

Focus of the inspection

The inspection focused on the production and control of Levofloxacin, Ritonavir and Vinblastine. The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients, including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging and Identification Labelling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls.

Inspected Areas

Day 1 started with an opening meeting. During the opening meeting the tentative inspection plan was discussed and confirmed. The company made a presentation about the site to be inspected. These presentations highlighted the company profile, the description of the site, a summary of manufacturing capacities, location of production of the various APIs, the site inspection history and major changes since the last WHO inspection. A copy of the presentation was obtained and will be filed in the company file at WHO.

Day 1
Opening meeting
Personnel
Quality Management: Product Quality Review, Risk Management, Change Control

Day 2

Quality Management:	Deviations, Complaints and recalls, supplier approval, document control, self-inspection, CAPA management, rejected materials, returned materials, reprocessing and reworking
Production:	Synthetics-VII
	API-III

Day 3

Warehouses:	Warehouse 2 , Central Warehouse
Production:	API-1
	Finishing and packaging block (non-cytotoxics)
Utilities:	Purified water system, WFI system

Day 4

QC Laboratory:	Chemical and Physical Lab - Sampling and sample handling, work allocation , specifications and test methods, SOPs, logbooks, records, worksheets and test reports, stability program, OOS results, evaluation of results, release and rejection procedures, chemicals and reagents, reference standards, retention samples, equipment, instruments and devices
	Microbiology Lab – Facility, media preparation, test procedures and results, OOS
Validation	Cleaning validation, process validation
Engineering	Preventive maintenance

2. QUALITY MANAGEMENT

The quality management system was generally well established, documented and implemented. The site organizational structure was reviewed and was acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified.

Product quality review (PQR)

PQRs were conducted on an annual basis according to SOP. 2013 APQRs for Rito Boc intermediate, Ritonavir, Vinblastine Sulfate Stage 1 and Vinblastine Sulfate API as well as Levofloxacin hemihydrate API were reviewed. All of the required elements had been considered and well documented, and were generally found acceptable.

In addition to the above mentioned SOP, local SOP required process capability to be determined for APQR. This was included as in the reports reviewed.

Quality Risk Management
Elements of risk management were referred to in several SOPs, e.g. the change control procedure. The SOP detailed requirements for risk management using FMECA as a tool. The scope of this SOP was appropriately wide and several example of applicability were given. Based on scoring for consequence, likelihood and detectability an RPN was calculated with action required to be taken if RPN<25.

A FMECA assessment of all Ritonavir processes from initial reaction to packaging was documented. Although generally acceptable, it was noted that some sections had not been completed. There was a slight concern about the objectivity of the scores allocated to detectability and this was discussed for future consideration by the company.

Out of specifications (OOS)
The general OOS procedure was reviewed and found to be acceptable. Selected OOS records were reviewed and showed that detailed investigations had been conducted and appropriate corrective action taken through the CAPA system.

Deviations
Deviations were handled according to SOP and covered planned and unplanned deviations. Deviations were classified as major or minor with examples of each provided. The above SOP had been revised due to the implementation of Pilgrim software for processing deviations. The manual and electronic systems were being run in parallel for 3 months.

A deviation to allow reprocessing a rejected batch was reviewed and was acceptable.

3. PERSONNEL

Personnel qualifications
According to the SMF, key personnel were suitable qualified with appropriate tertiary qualifications and extensive experience in the manufacture of APIs and pharmaceutical products.

Training
Training was conducted according to Cipla corporate procedures which were not reviewed again at this site. As an example of training and the records maintained, the job description and training records for a lab analyst that started with Cipla approximately 1 year ago were reviewed. These records were of a good standard.

Personnel Hygiene
Central washing, changing and toilet facilities were available. Requirements for entry to manufacturing areas were well documented with the level and type of protective clothing required dependent on the nature of the API and step of manufacture. Adequate change rooms were provided for entry to manufacturing areas with hand sanitization facilities provided.

4. BUILDINGS AND FACILITIES

Design and construction
Although an older facility, the design and interior finishes were suitable for API production and packaging. Non-cytotoxic API final finishing and packaging took place in a general finishing and packaging block that was provided with a Grade D environment.

Changing, toilets and washing facilities were provided in a central building. Entry to manufacturing and packaging areas was through appropriate change rooms.

Utilities
The operation of the HVAC system in the general packaging area was described in SOP.

Water
Purified water was produced by double RO and EDI by a modern unit. Distribution was through a stainless steel loop at ambient temperature. Weekly sanitization was performed. Sampling points were identified throughout the system. All records of maintenance, sanitization and monitoring were acceptable.

WFI was used in the final stages of vinblastine production and was produced by distillation with the distribution loop. All records reviewed for this system were acceptable.

Lighting
Lighting in all areas visited was acceptable.

Sanitisation and maintenance
All manufacturing areas visited appeared to be well maintained and clean. Cleaning and sanitization were performed according to documented procedures using materials approved by QA.

5. PROCESS EQUIPMENT

Design and construction
Equipment used for the APIs within the scope of the inspection was generally of a good standard and suitable for intended use. Where necessary to prevent cross-contamination, equipment for manufacturing Vinblastine was dedicated.

Equipment maintenance and cleaning
Equipment was maintained by the engineering department according to SOP. A schedule of equipment requiring maintenance and requirements for each equipment was documented.

As an example, the schedule, procedure and records for a fluid bed dryer were reviewed. These were acceptable.

Calibration
Where necessary, measuring equipment was labelled with a calibration tag. All of those reviewed indicated that the calibration was within date. The system appeared to be working effectively.

6. DOCUMENTATION AND RECORDS

Documentation system and specifications
A SOP described the procedure for creating QMS documentation, including SOPs. Requirements for authorizing documents were properly described.

Master documents were controlled according to SOP. These documents were required to be reviewed every 2 years or earlier if needed on a case by case basis.

It was stated that the site intended to implement a computerized system for managing documentation. Implementation time-frame is approximately 6 months with validation planned.

Equipment cleaning and use record
Procedures for cleaning equipment were available and the sample reviewed was acceptable (e.g. cleaning centrifuge bags). Log books were maintained for major equipment.

Records of raw materials, intermediates, API labeling and packaging materials
All records reviewed relating to materials, including intermediates and APIs were acceptable.

Master production instruction (master production and control records)
Master production batch records for each API were available. These were photocopied for use in batch manufacturing. Similarly there were master QC worksheets that were photocopied in the lab for use in batch testing.

Batch production records (batch production and control records)
The in-process BMRs and the completed BMRs reviewed had been properly completed and were generally acceptable.

Laboratory control records
The in-process QC records and the completed QC records reviewed had been properly completed and were generally acceptable.

7. MATERIALS MANAGEMENT

General controls
Suppliers of materials were required to be approved according to SOP. The approval process included a questionnaire, a sample for trial and analysis and audit of critical suppliers. An annual audit schedule was available. Critical suppliers were required to be evaluated every 3 years and others every 4 years.

The examples of suppliers reviewed showed that the procedure had been followed and records were acceptable.

Receipt and quarantine
Starting materials were received according to SOP. The procedure included cleaning of containers, a check for damage and a check for approved supplier. Material was then placed in dedicated quarantine areas. A separate warehouse (Warehouse 2) was available for cytotoxic starting materials and a -10 to -20^{o}C deep freeze was available for the key intermediate, vinblastine technical.

Sampling and testing of incoming production materials
Sampling of starting materials was performed by QC personnel according to a documented sampling plan. Appropriate environmentally controlled sampling areas were available in the warehouses.

8. PRODUCTION AND IN-PROCESS CONTROLS

Besides cytotoxics, no other toxic or hazardous substances (including β lactams) are handled on the site. Cytotoxics were properly handled in dedicated and self-contained facilities.

Production operations
Production operations in blocks API-I, API-III and Synthetics-VII were reviewed and generally found acceptable. Reactors were appropriately labelled with the batch in progress and the associated batch documentation was up to date.

Time limits
Time limits were specified in the Process Data Sheet where necessary. The SOP on holding time study for API and intermediates at in-process stage and holding time study of Ritonavir at in-process stages were reviewed and considered to be generally acceptable.

In-process sampling and controls
In-process sampling and testing was conducted as specified in the relevant Process Data Sheets ~~BMR~~. The IP test lab in block API-III was reviewed. Records showed that the pH meter here had been regularly calibrated and reference solutions were within use-by date. An IP TLC for Ritonavir was conducted here according to SOP.

9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging materials
Packaging materials were purchased from approved suppliers and placed in quarantine before sampling, testing and release by QC. The storage and labelling of these materials was acceptable.

Packaging and labeling operations
Packaging and labelling was performed in areas dedicated for this purpose. These areas were appropriately designed and classified, and routinely monitored. There was a documented line clearance check before packaging and labelling operations commenced.

10. STORAGE AND DISTRIBUTION

Warehousing procedures
Starting materials and APIs were stored in temperature controlled and monitored areas. The records of monitoring reviewed were acceptable. Packaging materials were stored in segregated areas with appropriate labelling and controls.

Distribution procedures
Documented distribution records were maintained. In the case of Vinblastine Sulfate, it was understood that data-loggers are used to monitor storage conditions during transport.

11. LABORATORY CONTROLS

General controls
The company had a well-organized and equipped QC laboratory.

Testing of intermediates and APIs
QC testing was conducted as specified in the relevant specification and according to documented test methods. Samples for testing were kept in a designated area and the relevant Section Head decided which analyst would do which test and what equipment to use. The hardcopy and electronic test records for a selected batch of levofloxacin were reviewed in detail and found acceptable.

Primary pharmacopoeial reference standards were available and working standards prepared according to a corporate SOP. The labelling and management of the standards was acceptable.

Stability monitoring of APIs
A range of stability chambers that encompassed WHOPQ requirements were available. Following initial stability studies to determine re-test date; at least one batch of API per year was required to be placed on on-going stability study.
The records for a batch of levofloxacin manufactured in 2013 were reviewed and found acceptable.

Reserve/retention samples
There was a designated temperature controlled area for storage of retention samples. Access to this area was restricted. A sample of each batch of API manufactured was kept here. Retention samples were stored in container systems that were comprised of the same materials as those used for the final API.

Handling of out of specification (OOS) results
The OOS/OOT handling procedure was available and considered to be acceptable.

12. VALIDATION

Validation policy
The company's validation policy was well described in a Validation Master Plan. This document required validation for new facilities, production equipment, utilities, systems, processes and procedures, validation to be verified at periodic intervals, and re-validation following a major change.

Responsibilities were well defined.

Qualification
Requirements for the qualification of equipment and utilities were included in the abovementioned Validation Master Plan. Periodic requalification was required at least every 5 years depending on criticality.

Process validation programme
There was a comprehensive validation matrix for all APIs and intermediates at Annex 2 of the abovementioned Validation Master Plan. This showed the recent history of validation, current status and the due date for re-validation.

Process validation for the production of ritonavir was reviewed and had been conducted according to Protocol. All process stages had been included with a separate report for each. The conclusion was based on a summary report of the 3 batches included and had been approved by all relevant personnel.

Periodic review of validated systems
Periodic review of validated systems was required by the above mentioned Validation Master Plan. This review was managed by the matrix of validated systems.

Cleaning validation
Cleaning validation was performed according to a generic cleaning validation protocol. Acceptance criteria were defined for residue of previous product (NMT 10ppm) and for cleaning agent (no trace in final rinse).

As an example, cleaning validation for ritonavir and a glass reactor was reviewed. The LOD of the test method and recovery had been determined. The results were well within the established limits.

13. CHANGE CONTROL
Change control was handled according to SOP. Changes were classified as major, moderate and minor with examples given for each. The need to notify regulatory authorities was included in the procedure. The current version included criteria for conducting risk assessment.

The current version of change control procedure was effective 1.2.2014 and it was noted that one of the new requirements was to formally consider the need for risk assessment.

14. REJECTION AND RE-USE OF MATERIALS

Rejection
Rejects were appropriately labelled and there was a locked dedicated area in the starting material and finished API warehouses for rejected materials.

Reprocessing
Where provided for in the Process Data Sheet, a step of manufacture could be repeated without specific approval if indicated by the results of an in-process check. This was recorded. In addition, examples were reviewed where the deviation system had been used to reprocess a batch that was OOS and e.g. the final purification step was repeated. This reprocessing required prior authorization.

Reworking
According to the APQRs reviewed, no reworking had been performed during 2013.

Recovery of materials and solvents
A solvent used in levofloxacin production was recovered with the process included in the Process Data Sheet. The recovered material was allocated a separate Item Code that restricted

its use to levofloxacin. It was collected in separate storage tanks and a sample tested by the QC lab before approval.

15. COMPLAINTS AND RECALLS

Complaints were handled according to SOP. They were categorized as technical or medical and the possibility of counterfeit was included.

A complaint about a batch of vinblastine was reviewed and discussed with the company at the time of inspection.

A SOP described the processes for handling recalls. Voluntary and statutory recalls were included in the procedure. There had been no recalls since the last WHO inspection. The abovementioned SOP was ambiguous regarding who made the recall decision.

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

No contract manufacturers or laboratories were used.

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, Cipla Limited located at Virgonagar, Old Madras Road, Bangalore 560 049, Karnataka, INDIA was considered to be operating at an acceptable level of compliance with WHO GMP guidelines for active pharmaceutical ingredients.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.