



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Cipla Ltd - Baddi
Unit number	NA
Production Block	NA
Physical address	Village Upper Malpur, P.O. Bhud, Tehsil Nalagarh, District Solan, Himachal Pradesh 173205, INDIA.
Contact address	Mr. Kishore Pathak, kishorepathak@cipla.com Tel.: +91-1795 246051, +91-1795 246045 Fax: +91-1795 246052 E-mail: baddi@cipla.com
Date of inspection	23, 24, 25 and 26 March 2009
Type of inspection	Routine Inspection
Dosage forms(s) included in the inspection	Coated and Uncoated Tablets with focus on HIV/HA and Anti-Malarial (MA) products.
WHO product categories covered by the inspection	Coated and coated tablets used in the treatment of HIV/AIDS and Malaria
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of Tablets.



Part 2: Summary

General information about the company and site

The facility inspected was Cipla **Ltd**, located at Village Upper Malpur, P.O. Bhud, **Tehsil Nalagarh**, District Solan, **Himachal Pradesh 173205, INDIA, here after called Cipla - Baddi**. According to the Site Master File, Version No.: GEN-02, effective 14.07.2008, Cipla Ltd has Corporate headquarters in Mumbai Central, Mumbai 400 008 India, plus manufacturing facilities and research centers in the following locations:

1. Bangalore : FPPs, APIs, natural products and Research Center
2. Patalganga : FPPs, APIs and Research Center
3. Kurkumbh : FPPs, APIs and Research Center
4. Goa : FPPs
5. Baddi : FPPs
6. Vikhroli : Research Center

Cipla Baddi is located in an industrial park off the Pinjore - Nalagarh road about 46km from Chandigarh airport. It was located on a 54200m² site of which 21597m² was built up. It had one production building (Block 4) with two floors:

- Ground floor: RM, PM and FG Warehouses, sampling rooms, dispensing rooms, QC laboratories and primary change rooms.
- First floor: Tablet, capsule, aerosol and pellet manufacturing plus their primary and secondary packaging.

According to the SMF, the plant employed a total of 461people: 248 in Production, 100 in Quality Control, 33 in Quality Assurance, 30 in Storage and distribution and 49 in Engineering and support services.

History of WHO and/or regulatory agency inspections

This was the first time the site of Cipla Baddi was being inspected by WHO Prequalification team. The manufacturing facility was licensed by the Drug Controlling-cum Licensing Authority, Himachal Pradesh (MB/05/110 and MNB/05/109, issued on 04.04.2005) to manufacture solid dosage forms (uncoated, film coated tablets, hard gelatine capsules and pellets) and inhalers (Pressurized Metered Dose Inhalers).

According to the company presentation, the site was approved by the Tanzania Food and Drugs Authority. It was also ISO 14001:2004 and ISO 18001:2007 certified.

Focus of the inspection

The inspection focused on the production and control of tablets with special focus on products used in the treatment of HIV/AIDS and malaria. 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.

Inspected Areas

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Day I

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards. They explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection including the WHO Public Inspect Report (WHOPIR) and Notice of Concern (NOC) and elaborated on the tentative inspection plan. After confirming the inspection plan, the company made a presentation about the company and the site to be inspected. The presentation highlighted the capacities, Quality Management System, product range and other specific features of the site. A copy of the presentation was obtained and will be filled in the company file.

This was followed by a review of the following documents related to quality management system.

- ⇒ Organization charts.
- ⇒ Job descriptions of key personnel,
- ⇒ SOP on Preparation of various lists, job responsibilities and Organization chart.
- ⇒ SOP on Control of Master Documents.
- ⇒ SOP on Creation, distribution, utilization, operation and destruction of SOPs.
- ⇒ Lists of SOPs.
- ⇒ SOP on Document and Data Control.
- ⇒ SOP on Generation and flow of BMRs and BPRs.
- ⇒ SOP on Batch numbering system (Formulations). The format of the batch number was \$#NNNN, where \$ = letter representing the site (D is for Cipla Baddi); # = end digit of the current year; NNNN = serial number from 0001 to 9999.
- ⇒ SOP on Batch split up.
- ⇒ SOP on Production Planning and Production Plan for March - May 2009.
- ⇒ SOP on Self inspection and Checklists.
- ⇒ SOP on Control on Logs, checklists and Formats.
- ⇒ SOP on Handling of Deviations. As an example, a major unplanned deviation occurred when some in process tablets were accidentally spilled onto the floor. A shortfall of 8% of theoretical yield was fully explained and the operator was retrained.
- ⇒ SOP on Change Control. Records for the several changes were reviewed.
- ⇒ SOP on Handling of Out-of-Specifications. A number of records for 2008 were selected for scrutiny:
 - ⇒ SOP on Batch release system of formulations.
 - ⇒ SOP on Excess material returns memo (EMRM).
 - ⇒ SOP on Part batch release.
 - ⇒ SOP on Reprocessing a batch

Thereafter, the following documents related to the site layout and utilities were reviewed, followed by an orientation tour of the site. These included:

- ⇒ Plot plan
- ⇒ Man and material movement layout, Ground Floor and First Floor.
- ⇒ AHU distribution, Ground Floor and First Floor.
- ⇒ HVAC system schematic drawing and summary of specifications for HVAC

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- ⇒ Qualification/Requalification/Monitoring the HVAC System. The qualification report (URS, DQ, IQ, OQ and PQ) of the AHU serving a compression Room, Blending Room, blend store and corridor and the AHU serving dispensary room were reviewed in detail.
- ⇒ SOP on Operation of Air Handling Systems
- ⇒ SOP on Filter Cleaning Procedures

The Water Generation and Purification System was reviewed starting with the drawings and summary of specifications and capacities. This was followed by inspection of the installations of the Water Generation and Purification System. Protocols, reports and records for the qualification and routine monitoring the PW system (Sampling and trend analysis) were reviewed.

The Effluent Treatment Plant was inspected plus related SOPs (e.g. SOP on Analysis of Effluent) monitoring records and trend of results.

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company and agreed on the tentative programme for the next day.

Day 2

The inspectors started by reviewing the progress of the inspection and outlining the days programme. They viewed the DVD of the airflow patterns in rooms served by AHU-179 during initial qualification. They proceeded to inspect the HVAC system at the service floors. Selected AHUs were inspected in detail. These included:

- ⇒ AHU serving compression, Blending room and blend store in manufacturing 8.
- ⇒ AHU serving compression III,
- ⇒ AHU serving pellet coating

Related SOPs were reviewed, including:

- ⇒ SOP on Cleaning of air filters of HVAC system.
- ⇒ SOP on Preventive maintenance of air handling unit.
- ⇒ SOP on Starting and stopping of AHU.
- ⇒ SOP on Duct leakage measurement.

The Compressed air system in the utility block was inspected along with a review of the summary of specifications for Compressed Air system, Protocol on compressed air sampling for the coating machine 2 and SOP on Preventive maintenance of air compressor.

The validation policies and schedule as stated in the Validation Master Plan (Version No. 01 of 2009) were reviewed. The following related SOPs were reviewed:

- ⇒ SOP on the hold time for dispensed raw materials, in-process and finished.
- ⇒ SOP on Hold time study and the following selected reports of hold time study protocols and reports:
 - Protocol for Binder hold time study.
 - Protocol for Lubricated blend hold time study.
 - Protocol for the Compressed tablets hold time study.
 - Protocol and Report for blend hold time for one ARV product conducted at Cipla Goa.

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- Protocol and Report for blend hold time for one ARV conducted at Cipla Patalganga.
- ⇒ SOP on Cleaning validation and establishment of worst case product.
- ⇒ SOP on Product transfer and Annexure on New transferred product manufacturing authorization.
- ⇒ Change control on site transfer of one ARV product from Cipla Patalganga
- ⇒ Change control on site transfer of one ARV product from Cipla Goa.
- ⇒ Change control on site transfer of one Anti-malarial product.
- ⇒ SOP on Risk management (Failure mode and effect analysis and Root cause analysis).
- ⇒ SOP on Validation and verification of analytical methods.
- ⇒ SOP on Analytical method transfer.
- ⇒ Validation of Dissolution of Artemether Tablets.

Process validation for the products in focus was reviewed and Qualification of Tablet press used to manufacture the anti-malarial product.

The schedule and service reports for the following equipment were assessed:

- ⇒ Tablet Press used to manufacture the anti-malarial product. Servicing followed an approved SOP. Details of the work to be carried out were given e.g. lubrication of parts, roller condition and hydraulic system checks. Originally, the weekly routine involved a brief clean up with a hydraulic pressure check. This schedule has now been upgraded to a more extensive programme. All time deadlines had been met and no matters of concern were noted.
- ⇒ Fluid Bed Drier: Its maintenance schedule details were given in two SOPs. One SOP detailed the functionality of the solid flow detector. The schedule for 2008 was reviewed. The records were satisfactory and it was noted that a more comprehensive schedule starting February 2009 is in place. A minor documentation error was noted in that the report related to the reference number of the form used. No matters of concern were noted.
- ⇒ Mixer Granulator: It was serviced according to the schedule in SOP. It was suggested that a check for the lid sealing gasket for wear and tear could be included because of possible fall out of foreign matter into in process granulate.
- ⇒ One of several metal detectors: The review was limited to the sensitivity of operation of the flap covering the reject chute. Its performance was checked daily using standard test pieces.

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company and agreed on the tentative programme for the next day.

Day 3

The inspectors started by reviewing the progress of the inspection and outlining the days programme. The following issues arising from the inspection AHUs the previous day were reviewed:

- ⇒ Deviation on marking the position of balance for dampers on three AHUs.
- ⇒ Deviation on labelling of supply ducts and dampers from one of the AHUs and change control on creation of area of low relative humidity using the AHU from areas previously served by another AHU.
- ⇒ Draft review of SOP on Cleaning of air filters of HVAC system.

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The cleaning validation policy and strategies were then reviewed in detail. The worst case assessment report was reviewed. The worst case assessment for FBE-500 and related cleaning validation report for one of the ARV products [equipment chain 33 for batch size 60,000 tabs and equipment chain 62 for batch size 150,000 tabs] were reviewed in detail. This also included review of validation of the HPLC and UV methods used during cleaning validation. The cleaning validation report [equipment chain 83 with batch size 400,000 tabs] for the FBE-500 with respect to the antimalarial product was also reviewed. Only one batch had been manufactured under the cleaning validation study.

The inspectors proceeded to review the vendor qualification system (SOP Evaluation and approval of manufacturer). Selected vendor audit reports were reviewed:

The inspection of the plant and production activities started with the change rooms, receiving areas, sampling areas, quarantine area plus warehouses for approved raw materials, primary packaging materials, secondary packaging materials and pre-printed packaging materials and the dispensing areas. SOPs and related records in these areas were reviewed, the following in detail:

- ⇒ SOP on Entry/Exit and Gowning Procedure (Change Room I).
- ⇒ Lists of personnel authorized to enter various areas.
- ⇒ SOP on Receipt of Raw Materials and Packaging Materials.
- ⇒ SOP on Cleaning and operation of Vacuum Cleaner and related cleaning log (S-049).
- ⇒ Print outs of the Approved Vendor List - Raw Materials from the ERP.
- ⇒ Balance daily calibration record and certification of the standard weights.
- ⇒ SOP on Operation of Reverse Laminar Air Flow.
- ⇒ SOP on Cleaning cubicles and related cleaning logs.
- ⇒ SOP on Sampling, testing, release and reject of Raw Materials.
- ⇒ SOP on Cleaning and usage of sampler and sampling devices (Raw Materials).
- ⇒ SOP on Dispensing of Raw Materials.

The inspector proceeded to inspect the production area and activities following the flow of production and packaging of coated and uncoated tablets. The related SOPs, use and cleaning logs, BMRs and BPRs were reviewed, the following in detail:

- ⇒ SOP on Cleaning of manufacturing area and related logs.
- ⇒ SOP on Preparation, usage, storage and destruction of disinfectants, cleaning and deactivating solution.
- ⇒ SOP on Cleaning and sanitization of washing area and drainage points.
- ⇒ SOP on Equipment Cleaning Fluidized Bed Equipment (FBE-500).
- ⇒ SOP on Equipment Operation Metal detector.
- ⇒ SOP on operation of Leak Testing Apparatus (ERWEKA).

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company and agreed on the tentative programme for the next day.

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The team started with a review of documents related to some of the outstanding issues from the previous day inspection. These included:

- ⇒ Hold time study protocol for the blend of the anti-malarial product.
- ⇒ Change control plus qualification and requalification reports for one of the AHUs.
- ⇒ Analytical method transfer SOP.

The system for product quality review was reviewed, starting with the SOP on Annual Product Review and the SOP on Product Review Reports. The Product Review Reports for two ARV products (for WHO) covering the three validation/registration batches each manufactured in 2008 were reviewed. There was no report for the anti-malarial product because the first batch had been manufactured in January 2009.

The team then proceeded to inspect the QC laboratory, starting with an orientation tour. Then the following areas of the laboratory were inspected plus review of the relevant documents, records and SOPs.

- ⇒ Packaging material testing laboratory:
 - Positive and negative films for carton labelling for the ARV products.
 - Pantone colour kit.
 - SOP on the Quality Control of Packaging Materials.
 - SOP on operating the Illuminated Magnifier
- ⇒ Sample receiving, storage and allocation procedure plus related records:
 - SOP on Sampling.
 - SOP on the Quality Control of Raw Materials (APIs and Excipients).
 - SOP on the Sampling and Analysis of Raw Materials (for WHO). The procedures for Identification, preparation of a composite sample and retention sample of received Raw Materials were reviewed in detail.
- ⇒ Training and competence qualification of analyst:
 - SOP about Training in Quality Control.
 - Analyst competence list and training programme.
 - Analyst Specimen signatures.
 - Training records of selected staff.
- ⇒ Wet chemistry laboratory (4)
- ⇒ Instrumental laboratory
 - Qualification, calibration, preventive maintenance
- ⇒ Laboratory materials management (Samples, Reagents, Stock Solutions, Reference and Working Standards)
 - SOP on Laboratory Reference Standards. The system for preparation, qualification, storage, issuance and use of Reference, Test and Working Standards was reviewed in detail.
 - Protocol and Report for Heat penetration and temperature distribution study for the Cooling Incubator with PLC.
- ⇒ Microbiological laboratory
 - Room and equipment
 - Media preparation and product testing
 - PW monitoring
 - Environmental monitoring
 - Validation of Sanitising Agents.

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- ⇒ Starting materials and finished products Specifications
- ⇒ Validation of Analytical methods
- ⇒ Stability chambers and stability testing programme
 - SOP on Stability Studies.
 - Stability Chambers charging and Withdrawal registers.
 - Mean Kinetic Temperature Study for Stability Walk in Chambers for the years 2007 - 2008.
- ⇒ Control samples

Records related to qualification, calibration and routine maintenance of laboratory equipment were reviewed, with detailed evaluation of records for randomly selected HPLC, UV visible spectrophotometer, Fourier Transfer IR, Dissolution Tester, pH meter, Karl Fisher and other auto titrators.

Records of sampling and testing selected APIs, excipients, finished products, components and packaging materials were reviewed.

The training policy, SOP, programme plus training records of specific sessions and selected individuals were reviewed.

The system for handling customer complaints (SOP, the customer complaints register and selected complaints plus the corresponding investigation reports were reviewed. This was followed by a review of the Product recall system (SOP) and related mock recall protocol .

The personnel hygiene policies (SOP) plus related checklists, correspondences and records were reviewed.

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection and gave feedback on the observations of the day. The company presented reports of some of the compliance actions they had either implemented or initiated and these were not fully evaluated. These included:

- ⇒ Change control on introduction of Pneumatic system for transfer of material into the sifter in Manufacturing 8.
- ⇒ Deviation on action taken with respect to the IPC container in "Cleaned Status" that was found with traces of powders.
- ⇒ Deviation on action to address drains that were found without water air-seal.
- ⇒ Proposed changes to be included in the VMP including a draft definition of "*Critical Equipment*" and clarity on the scope of application of Retrospective Validation.
- ⇒ Reconciliation of issuance of BMR/BPR, batch numbering system and designation of Date of Manufacture.
- ⇒ Review of the format and content of job descriptions of key personnel and their deputies.
- ⇒ Provision for trending of observations from self inspection reports.
- ⇒ Reconciliation of limits used in different documents of the Effluent Treatment Plant.
- ⇒ Reference numbering of organization Charts.
- ⇒ Reference numbering and assembly of various registers.

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The inspectors gave feed back and wrap up for the inspection and received reactions from the management of the company. There was consensus on all the observations made and conclusions reached.

2.1 QUALITY ASSURANCE

There was an organization chart and job descriptions specifying the responsibilities and reporting relationships of the various staff.

Equipment and systems had been qualified and procedures and processes validated. The quality of the systems, procedures and products were regularly reviewed and monitored through an elaborate self inspection procedure and annual product review.

All the routine procedures were guided by clear, written and approved procedures, any changes were controlled, deviations and Out-of-Specification results were documented, investigated and their impact assessed.

Change Control.

Change Control was managed by following a Corporate Quality Assurance SOP. A flow diagram to illustrate the procedure was appended. Changes were grouped as either documentation related (prefixed D), product related (prefix P), system related (prefix S) or facility based (prefix F).

The process started with identification of the need for change followed by impact analysis. Relevant departments were involved in the approval/rejection process. Regulatory aspects were also included.

Changes mostly related to documentation. Changes were monitored for affect and a period up to two years was allowed for a major change before close out e.g. a rebuilding project, but 3 months would appear to be the norm.

Deviations

Deviations were managed by following an SOP. Major and minor deviations were defined. There were sections on impact analysis, retraining, trends, CAPAs. Close out was required within 7 days for a major incident and 15 for a minor.

Out of Specification Results

Out-of-Specification results were managed by following an SOP. The procedure follows the conventional approach with sections on tracing assignable cause to laboratory error or production error. Details on sampling and re-sampling were given.

Selected reports were reviewed. In all cases the established cause was analyst's error. Retraining was effected and recorded.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

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Cipla Baddi had adequate and well maintained facilities for the manufacture and quality control of products under focus. There were adequately numbers of qualified personnel and the procedures used were comprehensive and well executed to ensure products of consistent quality.

Never-the-less, there were minor observations that required attention to further improve the degree of GMP compliance. Acceptable responses have been submitted to address the observations.

2.3 SANITATION AND HYGIENE

Cleaning procedures for equipment and the premises plus the waste management procedures in place were adequate to enhance hygiene on the site. Personnel were trained on how to maintain good hygiene. There were comprehensive factory entrance and changing procedures. The design of the HVAC and dust extraction system ensured a conducive environment for personnel and production and QC operations. Disinfectants of proven efficacy were used in sanitising premises and drains.

2.4 QUALIFICATION AND VALIDATION

There was a Validation Master Plan (version No.01 of 2009) which outlined the policy and approaches to be followed in qualification of equipment and validation of systems and processes. The approach qualification included definition of User Requirements Specifications (URS), Design Qualification (DQ), Installation, Commission, Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ). The conditions requiring requalification were specified as major changes, repairs following major breakdowns, changes in computer hardware or software, change in specifications or acceptance criteria, relocation of equipment. There were schedules for requalification, revalidation and preventive maintenance and records showed that they were being followed. Reports showed that equipment was qualified and systems and process were validated.

(a) Qualification of Compression machine

DQ/URS protocol specified the major requirements of the equipment which included but were not limited to compaction force and comprehensive punch and die specifications. Factory acceptance tests were included prior to installation.

Installation and operational qualification followed an approved protocol. The unit was supplied complete and only needed to be connected to the services required to operate it, namely electricity compressed air and the gravity feed hopper.

The OQ included exhaustive checks of compression settings, hourly tablet output, output at different rotational speeds and the performance of each station using a placebo batch. The machine was instrumented to a level which could detect an individual malfunctioning station when in operation.

PQ was conducted with compression three runs of established products. The machine was run at high and low speeds and the tablets tested. The criterion for acceptability used was the dissolution results. In all cases the results complied with specification.

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(b) Process Validation for the anti-malarial product

An approved validation protocol was followed. The process was developed at the Patalganga site and the validation batches were made in March 2008. Limited work was carried out at Baddi under a transfer of technology procedure, using three batches manufactured in February 2009.

Information on critical parameters, namely granulation, FBD, blend mixing times and compression forces were provided by Patalganga and a transfer technology team from there worked closely with the Baddi team during hand over. The equipment used was the same type at both sites.

No stability testing data was yet available for Baddi batches but the Patalganga data was reviewed. The protocol followed the ICH Guidelines and three lots were placed on stability. The 1, 2, 3, 6 month samples under accelerated storage at 40⁰C and 75%RH met specification in every respect.

(c) Validation of Dissolution the anti-malarial product

The dissolution technique was already established. Validation was more concerned with the HPLC detection of one of the APIs which is virtually insoluble in water. The capacity factor (ratio of analyte in the mobile phase to that in the stationary phase) is fundamental to HP and chromatographic separation. Practically this is shown on a chromatogram by the retention time of the peak of interest and the peak width. These will differ for replicate injections of the API if its solubility varies in the mobile phase.

Chromatograms showed no variability which in turn indicated a stable separation system. Linearity of detector response over the working range was satisfactory. Precision and accuracy were satisfactory.

Solutions were shown to be stable for up to 24 hrs with chromatograms of replicate injections showing constant peak height and shape and retention time. No matters of concern were noted.

(d) Cleaning validation

Cleaning validation studies had been done to validate cleaning procedures, hold times of uncleaned and cleaned equipment. Bracketing methods were used and an assessment was done to establish the worst case product (*poor solubility, highest strength and highest potency*) on the site, per production line and per equipment, which was then used to conduct the cleaning validation study.

The objective of cleaning validation was to reduce the bio-burden, residues of previous product, flavours from the previous product and residues of the cleaning agents. Swab recovery studies, analysis of rinse residues and microbial limit studies were used and the acceptance criteria used included: visually clean; absence of flavour odour; not more than 10ppm of residue of previous product; NMT 0.001% of the minimum dose should be found in the maximum dose of the next product; and NMT 50cfu/m³ bio-burden. Validated HPLC and UV analytical methods were used concurrently during cleaning validation. Three consecutive validation commercial scale batches were used in validation.

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It was provided that the cleaning revalidation was necessary in case a new product was introduced which affected the worst case evaluation, introduction of new equipment, change in cleaning procedure or cleaning agent. Other the validation status had to be re-verified every 5 years.

(e) Validation of Sanitising Agents

Cipla Corporate office had provided Baddi with the dilutions of sanitising agent they wished to be challenged.

The dilutions were shown to give 5 log reductions when challenged tested with 10^6 standard reference organisms. Swab recovery tests from different surfaces showed a 50% recovery (SOP). The company deemed this a satisfactory level. The writer has seen better elsewhere.

2.5 COMPLAINTS

There was a system to record, investigate and give feed back following receipt of market complaints. The selected cases reviewed were well investigated and appropriate corrective and preventive action taken.

2.6 PRODUCT RECALLS

There was a comprehensive recall procedure which classes of the deficiencies (critical, major or minor) that would require a recall had been defined together with the means of notification to be used, the timelines to conclude the recalls, levels of recall and the parties to be informed while conducting a recall. This was controlled by the corporate office for all Cipla Ltd sites.

There was a provision to evaluate the effectiveness of the recall procedures through simulated recalls at least once very year. Corporate office randomly selected one batch of any product from any Cipla site to be used in the simulation. No product from Cipla Baddi had been involved in the dummy recall so far.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The company did not carry out any contract production. Only specialized analytical procedures were contracted out and in such circumstances there was a contract that complied with the principles of GMP. The contracts defined the responsibilities if the contract giver and contract receiver, although it did not adequately specify how to dispose of left over samples.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self inspection procedures

There were procedures to conduct self inspection at least twice in a year for the purposes of monitoring the quality system and continuous improvement of the procedures. This procedure was comprehensive and the check list used covered all areas of production, quality control, quality assurance and engineering. There was a schedule with defined teams and records showed that the schedule was complied with.

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There were written reports in which deficiencies were classified as critical, major and minor. There were corrective and preventive actions taken, followed by evaluation by management.

Vendor Audit Programme

There was programme for evaluation and approval of suppliers which was managed under an approved SOP. The SOP allowed for the removal of any established supplier who subsequently fell short of requirements. The performance of vendors was reviewed annually and there was a procedure for requalification once every three years for APIs and once every 4 years for excipients.

There had been several editions of the SOP and the revision history of the SOP had become detached from the main document leading to some initial difficulty in matching the SOP requirement with the auditing process and its findings. This has been addressed.

Suppliers of all materials (not just APIs and excipients) were subject to vendor audits. A typical questionnaire was sent to all suppliers for basic information. It included requests for information on the buildings, the QC/QA and where applicable TSE free certification.

Audit reports for suppliers of the raw materials used in products submitted to WHO were evaluated. Audits had followed the SOP in force at the time and had been completed within ± 4 days of the scheduled date either by questionnaire or a site visit. The responses in questionnaires were adequate and the reports were comprehensive.

The one of the suppliers was marked 2 (acceptable) on an arbitrary scale of 0 to 3 and a SMF was provided. Despite Cipla being the API provider, the Patalganga site was nevertheless audited. The Irish source of one of the excipients was approved by questionnaire. The name of the technical auditor was missing from the Lumefantrine audit report.

2.9 PERSONNEL

The personnel met were well qualified to perform the duties assigned and had a high consciousness of GMP. There was an organization chart and job descriptions to guide personnel. The responsibilities of the key personnel like head of production, head of quality control and head of quality assurance were well defined and there were personnel designated to deputise the key personnel in their absence. The responsibility for batch review and release was assigned to head of QA.

2.10 TRAINING

The company had had a comprehensive training program for all the employees. This was coordinated by the QA department. New staff were given an orientation to the company and its products and underwent basic training including health, hygiene and safety regulations, basics of GMP and statutory requirements.

In-service training included operating instruction of production machines, Job related Training (SOPs Training), maintenance of BMRs and GLP training. The effectiveness of the training was assessed through training reports of the participants and questionnaires. Retraining needs were

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identified through performance reviews, self-inspection and audits. Records of training and practices witnessed or reviewed indicated that the staff were well trained and had adequate skills to perform assigned duties.

2.11 PERSONAL HYGIENE

Personnel were trained in personal hygiene procedure and facilities were provided in form of change rooms, protective garments and disinfectants.

The health of staff were monitored prior to employment and at least once a year through medical examinations. Staff with skin rashes, colds, communicable diseases, cuts or open lesions were required to report to the immediate supervisor and were not allowed in areas that may potentially contaminate the product.

Eating, drinking, chewing pan and smoking tobacco was prohibited in the factory premises.

2.12 PREMISES

Storage, production and testing activities were located in block No. 4. All storage, production and testing areas were accessed through primary changing rooms on the ground floor where factory clothing was donned. A “No jewellery” policy was in force. The change procedure was displayed on the wall. The toilet and washing facilities were located such that staff and visitors could use them before changing into factory clothing. Factory clothes were washed by a contract laundry service. The Technical Agreement with the laundry was valid for one year.

Raw and Packaging material receiving, sampling, storage and dispensing areas

The raw material, packaging materials and finished goods warehouses were located on the ground floor. The unloading area and quarantine were protected from the outside by air locks. There were separate sampling rooms for active ingredients, inactive ingredients and inactive liquids. The storage facilities allowed for effective segregation and security of materials and products at different stages of processing and those rejected. All goods were stored in high quality moveable racking. The area was regularly cleaned and temperature and humidity recordings were taken daily.

The temperature profile was ascertained by following an approved protocol. The number of monitoring points was calculated by taking the square root of the warehouse volume. The wet/dry bulb thermometers were evenly distributed throughout the warehouse and measurements taken with the AHU's in operation. The temperature range was set between 15⁰C and 25⁰C with the RH limit of NMT 60%.

A visual assessment of the data showed the temperatures throughout to be of the order of 25⁰C with no hot or cold spots. Corresponding wet bulb temperatures were not recorded but calculated RH values for each site reported. Without the wet bulb readings being entered it is impossible to confirm the RH values were in fact those stated.

Pest control was limited internally to insectocutors (Fly-O-cides) positioned over the entrances.

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The packing material store was similarly well maintained.

The cold store was a small controlled cupboard set amid the shelving. The temperature was well controlled between 2⁰C and 8⁰C. The system was audibly alarmed for excursions above 5⁰C. (Tested in the inspector's presence).

The dispensing rooms were accessed through air locks. The pressure differentials were set between 1.8Pa and 2.4Pa. At noon, it was noted that the early morning reading for the magnahelic gauge between dispensing booth 3 and the personnel air lock was showing marginally below 1.8Pa in comparison with the other gauges' readings which were showing a reading above 2Pa. This apparent anomaly had not been investigated. An acceptable investigation and corrective action have been undertaken.

Apart from the low pressure differential reading, no matters of concern were noted.

Production areas

Production activities were located on the first floor. The location, design, construction and maintenance of the premises were suitable to support production and storage of quality products. The design supported unidirectional flow of the manufacturing processing and there was adequate space for placement and operation of the equipment for the manufacture of tablets, capsules, pellets capsules and aerosols. The construction of the premises plus the installation of equipment and utilities enabled effective cleaning and maintenance.

There was a well designed HVAC system to provide a conducive environment for manufacturing and to avoid cross-contamination. Each manufacturing area had a dedicated AHU with temperature controls and 0.3 μ H13 terminal HEPA filters and there were dedicated dust extraction system. The exhaust from coating areas passed through a water scrubber.

Water purification system

(a) General

Raw water was supplied from a bore well to an epoxy lined concrete tank and dosed with sodium hypochlorite. The water was coarse filtered and softened before treatment with UV irradiation. The lamp was guaranteed for 7K hrs but was routinely replaced after 4K hrs. The operating voltage was set at 16K mv. Water was then treated to a second softening stage before RO and EDI treatment.

The water purification unit was compact and was housed in a dedicated room within the manufacturing block. Access was via the changing rooms and protective gowns, hats and booties had to be worn.

Engineering drawings and schematics were available for the water purifier. The unit was capable of producing 400 L/Hr (8K/day) and the projected usage at the time was of the order of 1.5x10³ L/day. There was a minimum of pipe work to maintain.

At the time of inspection, there was no distribution loop but it was the company's intention to install one at a later date. Meanwhile PW was transferred to the point of use in stainless steel (SS316) containers. The hold time had been validated up to 72hrs but in reality 2 hrs was the

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norm. Although the procedure did not contravene any GMP activity, it appeared to be cumbersome in its execution.

The plan of introducing the water distribution loop was to break through the ceilings and attach pendants followed by the necessary room requalification. It is recommended that WHO keeps this aspect in mind when reassessment is undertaken.

The PW unit was managed by following an SOP. The SOP covered details of operating the touch screen PLC controls together with instructions on how to pipe the water directly into a clean and sanitised stainless steel container before manually transporting to the point of use.

The unit was serviced according to the schedule in an SOP and pre-programmed maintenance followed an SOP. The actual maintenance schedule for the water purification system was not consistent with the one described in the SOP. No other matters of concern were noted.

The water produced had conductivity prior to EDI of 200 μ s and 0.43 μ s post EDI and on stand by. In use readings were recorded as 01 μ s.

The unit also supplied a storage tank for water to be used for generating pure steam. This tank was regularly sanitised with recorded F_0 values <20.

(b) Phase One Validation

The protocol followed the conventional procedure. URS, DQ, IQ, OQ and PQ were reviewed.

Design Qualification and User Requirement

URS were generated by the QA manager and the OQ specified the performance and operating characteristics. All parts were named including the water softening equipment.

Installation Qualification

This was undertaken by the unit's manufacturer and monitored by Cipla's engineering manager. The pipe work internal weld surfaces were certified as electro polished. All equipment had been calibrated as exemplified by the flow meter, pressure gauges on/off switch sensors and the conductivity meter.

Operational Qualification

The system was sanitised prior to OQ. All modules were checked for correct working. The relevant SOP had been finalized but was yet to be authorized.

Performance Qualification

PQ was satisfactory as demonstrated by chemical and microbiological test results. The water sampling procedure, microbiological tests and validation of the recovery and detection of the low levels of micro organisms anticipated, all followed approved SOPs. Samples could be kept for up to 2hrs before chemical testing and up to 8 hrs at 0 Deg C for microbiology.

The PW complied with IP, BP, Ph.Eur and USP requirements.

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Paragraphs 3.1.2 and 3.1.2 of the SOP detailed the procedure to be taken if samples gave TNTC results. They were not in the correct order. This error was corrected and authorized by Corporate before close of business.

Full documentation of media and growth promotion testing was recorded. For 28 consecutive days, samples from the sampling port and the flexible hosepipe used for filling the stainless steel vessel used in transport were tested. pH values were repeatedly 5.7 (spec 5.0 to 7.0), TOC 48ppb (spec 500ppb), raw data for bio-burden was between zero cfu/ml and 8cfu/ml. Pathogens were not detected. It was noted that the absence of fungi was not recorded. It was accepted that the company had yet to find any.

(c) Phase Two Validation

Samples taken twice weekly for 56 days were tested. Results were similar to phase 1. Testing was comprehensive in order to accommodate the differing requirements of IP, BP, Ph.Eur and USP. The alert limit was set at 50cfu/ml and the action limit at 100cfu/ml

(d) Phase Three Validation

Weekly samples again returned result similar to those of the previous validation phases. Trending of raw data showed consistently low levels with no significant spiking.

No matters of concern were noted throughout the whole assessment.

2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing products manufactured at the site. For tablet manufacturing, which was the focus of this inspection, these included vibratory sifters, Rapid Mixer Granulators, Fluid Bed Processor, Fluid Bed Drier, Multimill, Octagonal Blender, Single or double rotary compression machines, Auto-Coaters, blister/strip/container packing equipment with online batch coding printers. The product contact parts for all equipment were made up of SS316. Some production equipment was designed with PLC control systems and the related software had been validated.

The QC laboratory had enough glassware for wet chemistry and other instruments like HPLCs, GCs, FTIR and UV/VIS spectrophotometer and Auto-Titrators.

All equipment were generally well designed, had been qualified and they were regularly calibrated and maintained. There were use, cleaning and maintenance logs for each piece of equipment.

Pre-programmed maintenance

Maintenance of all equipment was carried out according to a set schedule specifying weekly, monthly and quarterly service requirements. The schedule and service reports for the several equipment (Tablet press, FBD, Mixer Granulator, Metal detector, etc) were assessed. No matters of concern were noted.

2.14 MATERIALS

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There was a system for development, qualification, dequalification and requalification of vendors of Raw Materials and Packaging Materials as described earlier. A comprehensive list of approved vendors existed and was always followed in procurement and receiving of materials reviewed.

All starting and packaging materials were tested and approved before they could be accepted for use. All containers of active and inactive materials were sampled and tested for identification. There was a procedure for making composite samples for other tests and the maximum number of samples that could be pooled was defined.

The storage conditions of all materials were defined and a list was available at the receiving area, intermediate storage areas and finish goods store to guide the staff to place the material in the right area. Granules, uncoated tablets and coated tablets were stored in sealed SS Intermediate Bulk Containers (IBCs) and their holding time had been validated.

Inventory Management System

An in house development computer system was used but only as a database for stock control. Status of goods was still controlled using a manual procedure involving status labels and QA/QC authorizing signatures.

Cipla Baddi raised an indent for materials, which was sent to central purchasing in Mumbai who then raised a purchase order with a copy to Cipla Baddi. The system would only recognize authorized suppliers by using a pre-programmed supplier number.

Goods were then dispatched to Baddi where a goods receiving procedure (SOP) was in force. Goods were checked against the purchase order (PO) before unloading. Certificates of analysis and TSE documentation must accompany the PO and challan. Records even included the delivery vehicle registration number. Variance in quantity delivered against that ordered was set at +10%.

Outer packaging was cleaned and removed and goods placed in quarantine and a copy of the GRN was sent to QC as a notification that sampling was required. Materials were recorded as individual lots and each separate lot was stored on its own pallet(s). The Goods in officer printed a bin card which was kept with the goods throughout its life cycle in the factory. QC allotted a sequential analytical AR number and printed out a corresponding “under test” label, which was attached to each container before sampling.

Upon completion of testing the appropriate status label (Approved/Rejected) was signed and attached to the container(s). The GRN was stamped “Passed” and given to goods in for their records.

The QC workstation had the capability to move raw materials in the “under test” fields to the “free stock” fields. This in theory would only permit the warehouse to issue approved materials, FIFO being a standard procedure.

It was noted that the dispensing procedure allowed for issue of materials pending final test results. This is considered a contravention of cGMP, even though it was documented as a deviation. The practice has since been dropped from the procedures.

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Stock close out followed the procedure in an SOP. The reconciliation limit was $\pm 2\%$ but the situation to invoke action had yet to occur. There was no investigational procedure available for guidance in the event of this happening.

Monthly cycle counts were conducted for class A items (APIs, other raw materials and packing materials). Other items (Class B) were checked annually. The system was randomly interrogated for individual stock records. The total holding of each material was broken down into individual lot Nos. Each transaction or return to stores was ascribed a reference number. The usage of a batch of one of the APIs was trailed. The residual stock in the computer listings was 5Kg .This tallied with the actual weight in stock. (Weighing requested by the inspector).

The system was automatically backed up every three hours and a daily record of transactions was placed on CD by the stores. The system satisfied the basic requirements of password protection, time out if unattended, and data entry verification. No problems were encountered throughout the inspection whenever any information requiring a computer interrogation was requested.

2.15 DOCUMENTATION

There was a procedure for preparation, review, approval and authorization of standard operation procedures. For products reviewed, there was a master formula, specification of starting and packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding results. The documents carried a unique number and their documentation, change and retrieval were well controlled by the quality assurance department.

There were some minor observations on the assembly of some, SOPs, record books and registers; compilation of some reports; clarity and cross-referencing of some SOPs and documents. Acceptable responses have been received towards these observations.

2.16 GOOD PRACTICES IN PRODUCTION

Production activities

Inspection focused on the manufacturing and packaging of coated and uncoated tablets. There were written procedures and records to manage the receipt, quarantine, sampling, labelling, storage and dispensing of materials; cleaning of equipment and premises; processing, packaging and distribution of products.

Any deviations from the approved procedures were investigated and their impact assessed before taking appropriate action. Limits for yield had been set at different stages of production and packaging and any results beyond the limits were investigated and documented.

The procedures employed in production included sifting using a vibratory sifter, wet granulation using a Rapid Mixer Granulator or Fluid Bed Processor, drying using a Fluid Bed Dryer while blending, direct lubrication in an Octagonal blender.



Compression was either single or double layers using single or double rotary compression machines, while coating was done in Auto coaters. The equipment used in processing and packaging had been qualified and the processing and cleaning procedures had been validated

Punch and die management

The compression tool store was kept in exemplary condition. All tools were coated with food grade oil and stored in numbered racks in locked cupboards.

An SOP gave guidance on purchase and receipt of new tools and their subsequent usage and maintenance. For new tooling the manufacturer provided pre-approval sets for authorization by QC. They were checked against authorized drawings and specifications. Extra punches and dies were ordered and the complete set was rotated to ensure even wear and tear.

The life cycle was governed by tablet type: 4×10^6 compressions for circular tablets; 2×10^6 for other shapes and double layer tablets; and 1×10^6 for effervescent tablets. The log usage for each set was kept in an individual register.

Full details of cleaning maintenance and inspection for wear and tear were available. Measuring equipment was calibrated.

The records for punches and dies for the products in focus were assessed and no matters of concern were noted.

Packaging

Tablet packaging was done either in strips (Alu/Alu), blisters (Alu/Alu, Alu/PVC, Alu/PVdC) or bottle containers.

There was limited activity at the time of the inspection. The packing hall was well laid out with primary packaging rooms operating under a positive airflow. Secondary packaging was a mixture of automation (cartons and PIL's) and manual (placing cartons into outer shippers).

The record of the on going packing process was audited. The blister-packing machine was operated using an SOP. Details of the clean down from the previous product and set up for the next were entered onto the packing record. Two operators checked the lot number set up and QC clearance to proceed had been given.

Components and tablets had been issued and checked before packing commenced. Reels of foil were checked for splicing before and during packing. The purchasing specification reportedly controlled the number of splices per reel.

Samples of foil, pre and post splice were included in the records when appropriate. Primary labels were monitored on line with bar code readers. All in process checks were up to date and endorsed with a QC signature.

Cartons were corded offline using locally sourced stereotypes. The procedure was exactly the same as that used at Patalganga. The purchase order stipulated the batch code to be engraved and the



quantity required. Each stereo was proof read before use. Excess/unused /damaged stereos were destroyed at the conclusion of a packing run. No matters of concern were noted.

Rework

Cipla's definition of reprocessing was to repeat the previous sub-batch process if the desired result was not achieved. Rework was the variation of an established process due to an unexpected deviation. The definitions did not allow for the addition of acceptable residues of a previous batch to a virgin batch and reworking was not included in the standard BMR format. To date no reprocessing or rework had been necessary.

Records were maintained to confirm that procedures were followed during production and to facilitate review before release. The SOP for batch release provided for the return of unused labels to store but there was no reference to any checks to ensure the absence of any overprinting (e.g. batch numbers) before returning. It was accepted that the release officer was aware of this and in the event of such an occurrence the rogue labels would be noted at the labelling set up for the next packing run.

2.17 GOOD PRACTICES IN QUALITY CONTROL

There were quality control and quality assurance departments whose functions were independent of other units including production. Quality assurance department was involved in approving new vendors for starting and packaging materials and equipment.

The quality control laboratory had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.

Raw material sampling and testing

Adequate sampling procedures and plans (SOP) were used for raw materials intended for WHO prequalified products and the testing procedures were documented and appropriately validated. All containers of active and inactive materials were sampled and tested for identification. A maximum of five samples could be pooled to make a composite.

Quality assurance staff reviewed all the production, packaging and testing records for each batch before it was released for distribution. Batch release followed an SOP and the head of QA was responsible for batch release. He had the necessary qualifications (Degree in Pharmacy), training, experience and authority.

Retention samples were kept from each batch of starting materials and finished products to facilitate any future investigation, if necessary.

Records of sampling and testing selected APIs, excipients, finished products, components and packaging materials were reviewed and found to be satisfactory.

Reference Standards

There were dedicated facilities (*LAF, humidity chambers, refrigerator and controlled boxes with desiccators*) for the preparation and storage of reference and working standards. The procedures

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for preparation of working standards were comprehensive (SOP). Reference and working standards were well labelled and the records for standardization of working standards were well maintained. Only RS with potency were used for assay and preservative content testing, while those without potency were only used for identification by IR. It was provided that RS and WS be stored in the fridge (2 - 8⁰C) and had to be allowed 30 minutes to equilibrate to room temperature before use. A limit of 60 minutes maximum exposure to ambient temperature at any one time was set. Access to the humidity chambers was password protected.

A batch of materials with an assay value of >99.5% and least impurity content was standardized against primary (pharmacopoeial) standards to prepare working standards. Triplicate assay were made. Records of selected RS and WS were reviewed and the system was generally found to be well managed.

Packaging Components

Components were sampled according to an SOP following the Military Standard/BSI 6001 guidelines. Samples were drawn for a level II inspection and normal rejection/acceptance AQLs were used in the decision chain.

All measuring equipment was calibrated. A Pantone colour reference was not always included in the component specification. Authorized standard reference samples for all components were held.

An aluminium foil was chosen for scrutiny of the testing record. PVC foil was similarly assessed. The records showed that the components were tested to specification with the AQL assessment indicating approval. No matters of concern were noted.

Chemistry Laboratory

The laboratory was well laid out with several separate rooms for wet chemistry and instrumental analysis. It was large enough to support a staff of 90 graduates. It was sufficiently well furnished and serviced and the fume extraction cupboards provided a satisfactory and certified airflow.

Sample receipt was recorded in a ledger and all details recorded they include but are not limited to Name supplier, Lot No. AR No. Lot No, date of receipt and date of approval/. Rejection. The QC manager distributed samples amongst the analysts based on each analyst's technical competence. Records of analysts' technical competence and training were available.

All wet testing followed compendial requirements and all reagents were prepared according to IP/BP/USP/Ph.Eur/in-house instructions. All preparations could be traced back to the bottle of solid reagent used.

Volumetric analysis was well documented and all standardisations complied with the relevant SOPs. All glassware was calibrated in-house or supplied with a calibration certificate.

Standard Laboratory Equipment.

Analytical balances were regularly calibrated across their working range. In-house servicing was limited in its range and no outside maintenance from any acknowledged specialists had been implemented. A service contract has been initiated.

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Tablet testing equipment, melting point apparatus, pH meters, Karl Fischer and other auto titrators were properly maintained and/or calibrated, as appropriate. The calibration and maintenance records of the dissolution apparatus chosen from several models were satisfactory. No matters of concern were noted

Instrumentation

(a) UV/Visible and FTIR spectrometers

UV/Visible and FTIR spectrometers were regularly calibrated. There was no outside contract maintenance to check the condition of vital components e.g. mirrors, choppers, gratings, and optical alignments. A service contract has been initiated.

(b) Gas-Liquid Chromatograph

A GLC was available for gaseous/residual solvent analysis but the equipment was not inspected.

(c) HPLC

Out of the several HPLCs installed, one was selected for review. There were qualification protocols for DQ/URS, IQ, OQ and PQ. The OQ report showed that it met the desired specifications for flow rate, detector wavelength calibration, linearity of response and auto injector performance. The software controlling the workings of the equipment was approved.

The reporting integrator was a data capture model with variable peak threshold setting. The operator set these after visual assessment of the initial chromatograms during set up. HETP, peak symmetry and resolution factors were automatically calculated and printed out. The peak efficiency in all cases gave well-defined start and finish integration points.

The HPLC column log was well maintained and managed using an SOP. HETP values were recorded after each usage. The data was used to decide whether or not the column was suitable for continued use.

Apart from lack of outside maintenance of spectrometers no matters of concern were noted. The chemistry section was well managed and staffed by very competent personnel. The facility and its equipment was a top class operation.

Microbiology

The facility was entered via a step over barrier where protective garments were donned. Without full gowning, entry to the plate pouring room and sterility test suite was forbidden. The walls of the laboratory areas were clad in 316 stainless steel. The facility operated under a positive air pressure relative to the outside with magnahelic gauges monitoring the prevailing conditions.

(a) Equipment

Incubators available were 22.5⁰C for fungi growth, 36⁰C for pathogens and 31⁰C for general applications. The temperature distribution had been validated and the oven temperatures were constantly monitored.

There was an autoclave for sterilizing media and equipment. It was subject to a regular validation and requalification which followed the requirements given in HTM 2010. The tests included

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empty chamber temperature studies, steam penetration, load configuration, vacuum and pressure hold times. The thermocouples used were calibrated externally. The sterilization cycle times consistently confirmed that the drain probe temperature remained at 120°C for a minimum of 15 minutes. F₀ values of the order of 29 were achieved.

A separate autoclave was used for destruction of used plates and unwanted media.

(b) Media preparation and use

A full range of solid media was stored and catalogued. Liquid media preparation followed an SOP. A preparation log was maintained and growth promotion tests, negative control results and the sterilization cycle reference number were included in the record.

Growth promotion was carried out with standard reference cultures. Standards were re-cultured after five generations.

The plate pouring room was a class C (10,000) and had a UDAF class A (100) with a horizontal air flow rate of 90 ft/min. (0.45m/sec).

No matters of concern relating to equipment and general microbiological practices were noted.

(c) Environmental monitoring

Both active air and settle plate samples were taken and an SOP was followed. The procedure stipulated the sample site, the frequency of sampling and the technique to use.

Settle plates were exposed for one hour and each site was checked every two months on a sequential basis. Typical results for the past 3 months were of the order of 30cfu/plate. The warning limit was set at 64cfu/plate and the action limit at 90cfu/plate.

For class B and C areas, 1m³ active samples were taken with an SAS18 while 50 litres were collected for class D areas. Results plant wide for the past 3 months were of the order of 72cfu/m³ and warning and action limits were 125cfu/m³ and 400cfu/m³ respectively.

No matters of concern were noted.

(d) Water testing

This is reported under Purified Water.

Stability testing

There was an adequate stability testing programme (SOP) supported by several stability chambers (25°C/60%RH, 30°C/65%RH and 40°C/75%RH) and a separate dedicated laboratory. Records of stability testing were maintained and could support the storage conditions and shelf life claimed for the products.

Records of charging, withdrawing and testing stability samples for the products in focus were reviewed and there was no major matter of concern noted. Batches of the anti-malarial product had been charged on 19th March 2009 and so no withdraw or testing had taken place.

Part 3: Conclusion

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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 Ltd, located at Village Upper Malpur, P.O. Bhud, Tehsil Nalagarh, District Solan, Himachal Pradesh 173205, 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

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.