



Annex B

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**

Part 1: General information

Name of Manufacturer	Calyx Chemicals & Pharmaceuticals Limited
Unit number	N-102, 91 & 90
Production Block	P I, PII, PIII, PIV, PV (for WHO pre-qualified products)
Physical address	MIDC, Tarapur, Boisar, Dist Thane
Contact person and email address.	Dr K.V. Walavalkar Kanhoba_walavalkar@calyxindia.com
Date of inspection	13 - 16 June 2011
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Pyrazinamide (APIMF078) Isoniazid (APIMF086) Artemther (APIMF120) Lumefantrine (APIMF121)
Summary of the activities performed by the manufacturer	Production and control of active pharmaceutical ingredients



Part 2: Summary

General information about the company and site

Calyx chemicals and pharmaceuticals limited was founded in 1979. The Tarapur facility started operations in 1979 and it manufactures various APIs and intermediates.

The company also provides contract research manufacturing services (CRAMS).

The company does not manufacture hormones, penicillins, cephalosporins.

History of WHO and/or regulatory agency inspections

The WHO had inspected the site in 2005.

The USFDA had inspected the site in September 2009 and raised seven observations in a Form 483. Subsequently the company's responses were accepted by FDA.

The EDQM inspected the site in September 2009 and suspended 3 of their Certificates of Suitability to the European Monograph (CEP); (for Pyrazinamide, Isoniazid and Zopiclone). They are due to re-inspect the site in September 2011.

Focus of the inspection

The inspection focused on the production and control of Pyrazinamide, Isoniazid, Artemether and Lumefantrine APIs. The inspection covered all the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1

- Introductions
- Attendance Record
- Confirmation of scope of inspection and inspection plan
- Company overview and presentation (about 15 minutes)
- Summary of manufacturing processes and product range
- Changes since last inspection and proposed changes.
- Production plan for the 4 days of inspection
- Responsibilities of the Quality Unit
- Responsibility for Production activities
- Internal audits (self-inspection)
- Product Quality review
- Change control
- Qualifications
- Training



Day 2

Materials management

- General records
- Inspection of Receipt and quarantine
- Sampling and testing of incoming production materials
- Storage
- Re-evaluation

Buildings and Facilities

- Design and construction
- Utilities
- Water
- Containment
- Lighting
- Sewage and refuse
- Sanitization and Maintenance
- Inspection of AHUs

Day 3

Packaging and identification labelling of APIs and intermediates

- General
- Packaging materials
- Label issuance and control
- Packaging and labelling operations

Process Equipment

- Design and construction
- Equipment maintenance and cleaning
- Calibration
- Computerized systems

Storage and distribution

- Warehousing procedures

Laboratory controls

- General controls
- Inspection of labs
- Testing of intermediates and APIs
- Validation of analytical procedures
- Certificates of analysis
- Stability monitoring of APIs
- Expiry and retest dating
- Reserve/retention samples
- Primary and working standards
- Instrument maintenance



Day 4

Documentation and records

- Documentation system and specifications
- Equipment cleaning and use record
- Records of raw materials, Intermediates, API labelling and Packaging Materials
- Master production instructions
- Batch production records
- Laboratory control records
- Batch production record review

Validation

- Validation policy
- Validation documentation
- Qualification
- Approaches to process validation
- Process validation programme
- Periodic review of validated systems
- Cleaning validation
- Validation of analytical methods

Rejection and reuse of materials

- Rejection
- Reprocessing
- Reworking
- Recovery of materials and solvents
- Returns

Complaints and recalls

Contract manufacturers (including laboratories)

CAPA

Closing meeting with company representatives

2.1 QUALITY MANAGEMENT

In general, the quality system encompassed the organization structure, procedures and processes which were in place. The quality unit was independent from production areas, however quality control laboratories were physically housed inside the production areas. There were two persons (VP QA/QC and Senior Manager QA) authorised to release the APIs.

The SOP for internal audit and internal audit schedule were reviewed. The maintenance/engineering department was not included in internal audits. It was stated in the SOP that audit team comprises of representatives from the department other than that being audited, however in many instances, CQA audited their own CQA. Similarly, according to the latest schedule, it was observed that the deputy manager of EHS was to be the part of the team to audit EHS and engineering departments. Moreover, audit team was composed of 2 members of personnel/auditors. The checklist for internal audit was not



comprehensive e.g. key production areas were not included. The SOP for internal audit didn't state clearly the timeframe for remedial action or for close out.

Quality manual: This was an overall document explaining the company philosophy. The topics covered included contractors and environment controls; however no references to any guideline were made.

The SOP on handling of deviations was found inappropriate in paragraph "4.12 participate in the investigation of deviations discrepancies or test failures" and "4.23 any other assignment allocated". The job description of Dr Trivedi, Vice President QC/QA had the overall responsibility and key areas were explicitly stated. The specified deputy was Mr K Kore.

The SOP described 40 responsibilities including all those specified in the WHO GMP for APIs (for Mr Nair, production head).

The SOP on product quality review was reviewed. The SOP didn't provide any detail on how product quality review was to be carried out, type of tests to be reviewed, statistical analysis and their acceptance criteria. Also, there was no specific template available to ensure PQR was carried out for all products consistently.

2.2 PERSONNEL

Personnel met during the inspection were found to be experienced, knowledgeable and competent in the task assigned to them.

The training was covered in two SOPs, one induction training SOP, and another one on training SOP. For Induction training, new employees were given a manual ITM/01, effective date 01/12/10. After reading, they were required to return the manual. This document gave a good introduction to the company and the procedures. The effectiveness was assessed by the employee answering 15 questions which were a mixture of multiple choice and having to select between "true" and "false". For training, each department was responsible for its training schedule and its implementation.

The responsibilities of key personnel were described in the job descriptions.

Based on the number of issues noted in the quality assurance / quality control department, it appeared that number of personnel were not adequate to carry out quality assurance tasks.

2.3 BUILDINGS AND FACILITIES

There were examples of poor standards of maintenance. Wall finishes were seen to be poor. Some process pipes were poorly installed. However, some refurbishment work of Plant 1 was undertaken about 6 months before the inspection. Overall, this resulted in acceptable standards of the production buildings and equipment.

It was noted that Plant V (used for the production of Lumefantrine) was under construction at the time of inspection. The inspection team made a brief tour of this plant.

In many instances, it was seen that different materials and same material of different batches were stored on the same pallets which might cause mix ups.

The liquid dispensing area was found to be inadequate in that no proper ventilation system existed to handle various organic solvents.



Quality control was independent from production from responsibilities and management point of view. However, laboratory areas were housed inside the production areas which might compromise conflict of interest. It was recommended to physically separate laboratory areas from production areas.

The utilities, in particular air handling units and the purified water systems were found to be adequate in general.

Plant 1, 2 & 3 manufactures Pyrazinamide, Isoniazid and Artemether on a campaign basis, while Lumefantrine was manufactured in a separate Plant.

In some instances, lighting was not found adequate. Some of the ceiling lights were found out of order during the inspection.

There were two SOPs in place for pest control. "Rodent and pest control" and "cleaning of areas before and after pest control. These two SOPs were not cross referenced. There was no mechanism by which this was ensured. The records were stored with the administration department.

2.4 PROCESS EQUIPMENT

In general, equipment (reactors, centrifuges, dryers, blenders, milling machines etc) used in the manufacture of APIs were found to be appropriate in terms of design, material of construction and capacity.

It was noted that full sets of drawings were not available for inspection.

The index for maintenance SOPs comprised of three sheets with different dates. For detail, refer observation section below.

The instruments / equipment were periodically calibrated and calibration tags were placed on the respective equipment.

The manufacturing processes were manually operated and there were no computerised systems used to control manufacturing processes at various stages.

2.5 DOCUMENTATION AND RECORDS

It was noted that the company had more than 800 SOPs for various operations. However, the documentation system was found to be inadequate in many aspects.

- There were several SOPs available on the same subjects and there were no cross referencing made.
- Various SOPs were found inadequate. For e.g. SOP on out of specification (OOS), product quality review , complaint handling, SOP on SOP (document control) etc
- Corrections to entries were made without ensuring original entry remains readable
- Logbooks for some of the key operations such as log of OOS, and HPLC column usage record etc were not maintained.
- There was no record maintained for approved labels (green) issued by the quality control laboratory
- The batch production records of APIs didn't state some of the key process information and their specification/range
- Temperature records of various areas didn't bear limits / acceptance criteria.



2.6 MATERIALS MANAGEMENT

The SOP on vendor certification was reviewed. Following key starting materials were qualified based on the on-site inspection:

- 2-cyanopyrazine
- Artemisinin
- DDFE (used for Lumefantrine) intermediate produced at Calyx Ambernath site (didn't evaluate / inspect site). It was noted that only this intermediate was manufactured at Calyx' Ambernath manufacturing site.
- MOF (used for Artemether): not qualified yet, however SOP require key starting materials to be qualified after on-site inspection.

The approved vendor list for Lumefantrine and Isoniazid was not updated every six months as required in the SOP. Similarly, addendum (annexure VI) was not revised after inclusion of new vendors.

The retesting of APIs was found inadequate as one of the APIs was due for retest in May 2011; however the status was not changed and it was stored in the approved materials area instead.

It was also noted that not all four APIs bore specific storage conditions.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

The solid starting materials were weighed under controlled conditions and dispensed to "day store" before being used in the production. The dispensing area in general was found acceptable.

The liquid dispensing area was found to be inadequate as it was not controlled to ensure suitability for use. A limited supply of filtered air was being supplied to the area where solvents were dispensed. Also, access to the room was directly from the outside (no lobby, or clothing requirements). Whereas the potential for exposure of the solvents/liquid reactants to contamination was limited, due to the size of the openings in the drums, there was an inconsistency with the sampling of solids, which was done within an RLAF booth (although there were deficiencies associated with this).

The weighing operations were signed off by the person who carried out the operation and was checked by other personnel.

The actual yields of Pyrazinamide for some of the batches were found on the lower side against their specification. The deviations were raised but investigation was found inadequate and root cause attributed to production problem.

There was an ambiguity noted on the reprocessing and reworking of APIs. It was noted that the company didn't carry out reworking.

The blending of left over materials (tailings) of APIs was carried out. However, this appeared to be inadequately controlled and documented.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The APIs were packed in double polyethylene bags before finally packed in HDPE or fibre drums depending on the stability study and/or customer requirements.



2.9 STORAGE AND DISTRIBUTION

In general, the finished product store was found to be acceptable and maintained adequately.

2.10 LABORATORY CONTROLS

In general, the laboratory facility was equipped with modern equipment and instruments.

The QC and production personnel had a common changing area and access to their respective areas. Entrance to the main QC lab was from the same corridor and within 2-3 metres of Plant III uncontrolled area, Plant III day store and the entrances to the controlled areas of Plants I & II. From a nearby stairway, (which also gave access to the changing room mentioned above) there was access to the retained samples room, whilst the stability chambers and HPLC room were reached by going through the room housing part of the water purification equipment.

The documented procedures were in place for sampling of incoming materials, intermediates and finished products.

As there was no OOS log available for 2010, it was difficult to ascertain how many OOS results were raised in 2010 and investigated appropriately. Nonetheless, the SOP on out of specification was found inadequate. The following issues were noted:

- OOS flow chart didn't tally with investigation process described in Phase I & II
- Revision history didn't provide any detail on changes made in the latest version
- OOS log for 2010 was not available for inspection

The storage of primary and secondary reference standards was found inadequate. Lumefantrine USPRS required to be stored at controlled room temperature, however it was stored in the refrigerator (2 to 8 C) instead.

Similarly, standardization of working standard of Lumefantrine was found inadequate. The working standard was not standardised against the USPRS, though available since 2006. Moreover, Lumefantrine was not adequately characterised knowing it exhibits polymorphism. The tests for description, loss on drying, related substances and assay were carried out. The assay was carried out in duplicate.

The microbiology laboratory conducted water analysis, environmental monitoring and microbial limit test.

The retention sample room was found inadequate. For more information, refer observation below.

Some of the liquids and solids sampling tools were not wrapped correctly. Also, there was no status label available as to "clean" or "to be cleaned".

Stability study

The SOP on stability study for API and intermediates didn't state a window period for the withdrawal of stability samples. The real time and accelerated stability study data for Lumefantrine (double HDPE bags and fibre drum) were reviewed and it was noted that only 12 months real time data were available against the 4 years shelf life proposed. There was no trending carried out though loss on drying was found to be increasing from 0.21 to 0.36% in 12 months. There was no intermediate study conducted at 30C/65% on Lumefantrine. The 12 months stability study data for the above three batches were reviewed. It was noted that total impurities and loss on drying were found to be increasing. The audit trail was not activated.



The stability study data of Pyrazinamide conducted at (25C/60%, available up to 72 months) were found satisfactory.

Artemether stability study data for long term stability (2 - 8 C) were available for 24 months against 5 years of shelf life only for two batches. There was no trending carried out though loss on drying and total impurities were found to be increasing.

Isoniazid long term stability study (25/60%) was conducted on three consecutive batches and 36 months data were available for review. The loss on drying and total impurities was found to be increasing, however no action was proposed.

2.11 VALIDATION

The process validation document of Lumefantrine was briefly reviewed. The concurrent process validation of Lumefantrine was performed taking into account the critical process parameters listed in the validation protocol. There was some ambiguity noted in the process validation protocol and report of Lumefantrine. The company was requested to provide clarification.

The validation master plan was reviewed. A thorough overall document, however annexure 1 for the water system sampling plan was different to that in the water system document. There was no formal revalidation procedure available, although there was a reference to the revalidation in the VMP.

An example of cleaning validation was reviewed for SS reactor R1 - specifically on process change from Zopiclone to Pyrazinamide. This was a thorough document including a drawing indicating swabbing points.

The document on cleaning of FBD 1 during production of Pyrazinamide and product change over was reviewed. The details were recorded in the batch cleaning record. In general, cleaning was found to be satisfactory.

It was noted that blending of left over material (small remainder after the bulk of the batch had been packed) was not validated.

2.12 CHANGE CONTROL

Change Control was covered in SOP. All departments were covered and the requirements were comprehensive. An example was reviewed regarding adding total impurities to the stability reports of Pyrazinamide. The details were observed to be in compliance with the SOP.

2.13 REJECTION AND RE-USE OF MATERIALS

There was no distinction made between reprocessing and reworking. The reprocessing of intermediates failing specification was detailed in SOP.

2.14 COMPLAINTS AND RECALLS

SOP on handling of complaints was reviewed. In general, this area was found to be inadequate.



2010: Isoniazid complaint received was not recorded in product quality review. The log of product complaint didn't have SOP reference number.

The complaint was not adequately handled as no root cause was determined and no CAPA was proposed. The batch numbers seen on the IR spectrum was different from the actual batch numbers in question.

2011: Lumefantrine and Pyrazinamide complaints were reviewed. The log of product complaint wasn't filled in appropriately as category was filled with expiry of the product. Also, priority assessment stated immediate instead of urgent or routine.

The Lumefantrine complaint wasn't handled adequately. The complaint was with regard to the high moisture content and poor flowability. However, the complaint was not investigated knowing that Lumefantrine exhibits polymorphism. There was no root cause identified.

As per SOP, the complaint was supposed to be handled and closed within 30 business days, however it was not the case.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The SOP on certification for OFF site testing laboratories was reviewed. It was noted that 7 laboratories (Choksi, Vapi, IIT, Powai, Manisha Analytical Lab, Kandivali, Amol test laboratory, Boisar Intertek, Andheri, Geochem and Hexa lab, Mumbai) were used to carry out testing for Calyx products. However, the technical contract between laboratories and Calyx was not available.

The SOP on certification for OFF site testing laboratories stated that contract laboratories were to be selected based on the proximity instead of their capabilities.

The SOP for review of batch manufacturing records and API/intermediate batch release for market purpose was reviewed. It was found that Mr. K. Kore and Dr M. Trivedi were responsible for the final release of batches for dispatch. The batch was reviewed by Mr Sayed Nazeer (QA) and signed off by Mr Kore.

The BMRs for Pyrazinamide, Artemether, and Lumefantrine were reviewed. The Batches were reviewed by Mr. Sayed Nazeer who joined the organization on 14th March 2011 (with little experience) and signed off by the senior manager QA. As per the release procedure, the VP QA (Dr Trivedi) was responsible to release the batches; however he didn't review and sign off the batches.

The batch record template of Artemether was changed and approved by Mr. Kamlesh instead of Dr Mithilesh.



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, APIs (Pyrazinamide, Isoniazid, Artemether and Lumefantrine) manufactured at *Calyx Chemicals and Pharmaceuticals Limited, India* were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.