

Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient (API) Manufacturer

PART 1: GENERAL INFORMATION

Name of Manufacturer	Calyx Chemicals & Pharmaceuticals Ltd
Unit:	Unit I and Unit II
Plant:	Plant I, II, III, IV, V, VI & VIII
Physical address	N-102, 91&90, MIDC, Tarapur, 401 506 District Palghar, Maharashtra, India
Date of inspection	22 – 24 June 2015
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	– Pyrazinamide (APIMF078) – Isoniazid (APIMF086) – Artemether (APIMF120) – Lumefantrine (APIMF121)
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished APIs

PART 2: SUMMARY

General information about the company and site

The Calyx Chemicals and Pharmaceuticals Limited was founded in 1979. The Tarapur facility started operations (manufacturing of active substances and intermediates) in 1998. The site consisted of two units and 8 plants (Plant I, II, III, IV, V at Unit I, and Plant VI, VII, VIII at Unit II). There were 18 active pharmaceutical ingredients licensed and 5 active pharmaceutical ingredients regularly manufactured for the domestic and export markets. The cold chambers for finished products requiring controlled temperature (2-8 °C), stability chambers, retain sample store (samples up to year 2010) and a document archive were located outside (about 500 m distance) of the inspected site on the address: M-4, MIDC, Tarapur, 401 506, District Palghar, Maharashtra, India (not covered by the inspection).

The site did not manufacture hormones, penicillin's and cephalosporin's.

History of the WHO and/or regulatory agency inspections

This was the fourth WHO inspection. Last WHO inspection was conducted from 5 to 8 May 2014. The site had been inspected by the following authorities:

- United States Food and Drug Administration (US FDA):
 - 2009
 - 2012
- European Directorate for the Quality of Medicines & HealthCare (EDQM)
 - 2009
 - 2011
- Swissmedic
 - 2011

Focus of the inspection

The inspection mainly focused on the production and control procedures of:

- Isoniazid (APIMF086)
- Implementation corrective and preventive actions from the last WHO inspection.

Inspected Areas

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls

PART 3: INSPECTION OUTCOME

3.1 QUALITY MANAGEMENT

Principles

In general, a system for managing quality was established, documented and implemented. The quality unit was independent of the production department. The person responsible for release of intermediates and APIs was specified.

The associate vice president Quality Assurance (QA) /Quality Control (QC) joined the site recently before the inspection. The associate vice president Quality Assurance (QA) / Quality Control (QC) job description was reviewed.

Product quality review (PQR)

The SOP “Preparation of annual product review (APR)” was reviewed. APR schedule for 2014 was checked. According with the SOP APRs should be ready preferably before the end of February. If the API was manufactured with different processes, then separate APRs were prepared. According with the SOP trend analysis should be based on statistical calculations (3 sigma and 4 sigma). For statistical calculations SPC XL (Microsoft Excel) software was used.

The APR for Isoniazid for 2014 and trends for finished API were reviewed.

The SOP “Quality risk management (QRM)” was checked. The SOP was applicable to assessment and management of the Quality and compliance risks associated with products across the product lifecycle. The tools specified in the SOP were:

- SWOT (strengths, weaknesses, opportunities and threats) analysis
- Process mapping
- Ishikawa diagram
- Brain storming
- Risk ranking and filtering

The risk assessment (RA) register was not available. It was said that the Risk Analysis (RA) was carried out for all products using Risk ranking and filtering.

The RA and evaluation record for Isoniazid was checked.

The SOP “Review of batch manufacturing records (BMR) and release procedure” was reviewed. The head production or authorized representative was responsible for review of the Batch Manufacturing Records (BMR).

- The head the QC or authorized representative was responsible for review analytical records / certificate of analysis
- The head the QA or authorized representative was responsible for final review of BMR analytical records for release.

The following check lists were used:

- Review of BMR
- Review of analytical reports.

3.2 PERSONNEL

The total numbers of employees involved in the site was 153, from which 8 were involved in QA activities, 28 in QC activities and 60 in production activities. Contract workers (60 - 70) were involved in housekeeping of the clean rooms, material transfer, general housekeeping.

Contract workers

The contract labour workers were allowed to enter classified areas. According with the company explanation contract labour workers were involved in cleaning activities in the cleanrooms, material transfer and housekeeping.

The SOP “Personnel hygiene” was checked.

The SOP “Procedure for medical check-up” was also checked.

The SOP “Training” was spot checked. SOP did not cover contract workers training.

The contract workers training records and health checks were requested. Medical health checks for contract were not presented.

Medical health checks were presented for the permanent employees for 2013 and 2014.

3.3 BUILDINGS AND FACILITIES

Design and construction

The production and warehousing areas did not change since the last WHO inspection.

The recent inspection focused on the specific powder processing areas.

Utilities

The air handling units (AHU) were installed to control the environmental conditions in the powder processing areas. The blueprint, monitoring and functioning of AHU 5 and AHU 4 were checked. The AHUs were regularly tested (performance qualification 2 times a year, revalidation every 5 years).

Containment

Highly sensitizing materials were not manufactured on site.

Sanitation and maintenance

The SOP sanitation was discussed.

3.4 PROCESS EQUIPMENT

Design and construction

The equipment used in the manufacture of intermediates and APIs did not change since the last inspection.

Equipment maintenance and cleaning

Schedules and procedures were established for the preventive maintenance of equipment. The cleaning procedures were available for operators to clean each type of equipment. The equipment was identified as to its contents and its cleanliness status.

Computerized systems

Computerized systems were not used in production. The laboratory instruments (High Performance Liquid Chromatographs - HPLC and Gas Chromatographs - GC) were stand-alone instruments. The chromatographic data were backed up daily and archived in the server every three months. After the archiving the data were deleted from the data acquisition computers.

The SOP “Backup and retrieval of electronic technical data & review of audit trail” was reviewed.

The SOP “Computer access control” was spot checked.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. The specifications were established and documented for raw materials, intermediates, packaging materials and finished APIs. The master list of documents (SOPs) was available.

Batch production records (BMR)

The batch production was recorded in the batch production records. The batch number contained the product code reflecting the molecule.

3.6 MATERIALS MANAGEMENT

Sampling and testing of incoming production materials

The SOP “Sampling of raw materials, packaging material, in-process material, intermediate & active pharmaceutical ingredient” was spot checked.

Suppliers audit and approval

The SOP on vendor qualification was checked. The approved vendor list was also discussed.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

The production operations were performed in different multi-product manufacturing plants.

Blending batches of intermediates or APIs

The SOP “Blending of material from different lots / batches to make suitable batch size” was spot checked. According with the SOP expiry / retest date shall be considered of the oldest batch taken for blending considering the fact that minimum retest period of the finished product shall be at least 1 year.

The Batch Manufacturing Record (BMR) for left over material Isoniazid batch No XXXX was reviewed. The left overs of 8 batches were blended. The oldest batch in the blend was manufactured in April, 2014. Expiry date for Isoniazid was 5 years. Blended batch expiry date was specified March, 2014.

The blending validation report for Isoniazid batch size XXXX kg was spot checked. 3 batches of Isoniazid were used for the study.

Deviations

The SOP “Deviation and investigation” was checked. Deviations were categorized as:

- Critical
- Major
- Minor

The deviation registers for 2014 and 2015 were reviewed.

The deviation No XXXX was reviewed. During deviation investigation the root cause was identified and CAPAs specified.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The procedures did not change substantially since the last inspection.

3.9 STORAGE AND DISTRIBUTION

The procedures did not change substantially since the last inspection.

3.10 LABORATORY CONTROLS

The instrumentation and basic procedures of the QC laboratory did not change since the last inspection. The stand-alone Personal Computers belonging to the chromatographs (HPLC, GC) were connected to the server.

The Isoniazid, British Pharmacopoeia /European Pharmacopoeia/United States Pharmacopoeia, batch No XXXX analytical report was spot checked and assay calculations re-calculated. Print outs of HPLC chromatograms were compared with the electronic raw data.

Out of specification (OOS)

The SOP “Out of specification” was checked. The procedure was applicable for OOS tests of raw materials / packaging materials, intermediates APIs and stability study samples. In-process OOS results were handled as per the SOP deviations”.

A specific OOS investigation reports were checked.

3.11 VALIDATION

Validation policy

The validation policy was summarized in the validation master plan.

Analytical method validation

The analytical methods were developed and validated by the R&D in Dombivli then transferred to Tarapur if applicable. The SOP “Analytical method transfer” was checked.

3.12 CHANGE CONTROL (CC)

The SOP “Change control” was checked. SOP was applicable for:

- Starting materials
- Process
- Batch size
- Process equipment
- In process control
- Intermediates
- Primary and secondary packaging materials
- Analytical specifications and test procedures
- Cleaning procedures
- Vendors
- Manufacturing facilities
- Utility
- APIs
- Other documentation

Changes were categorized as:

- Minor
- Major
- Permanent
- Temporary

The CC registers for 2014 and 2015 were checked. CC registers were managed by the QA department.

3.13 REJECTION AND RE-USE OF MATERIALS

The SOP “Re-processing of intermediates and APIs failing to meet established specifications” was checked. According with the SOP reprocessed / reworked batches shall be kept for accelerated stability studies.

The list of reprocessed, rejected and reworked batches for 2013, 2014 and 2015 was presented to the inspectors.

The SOP “Policy for recovery of solvents, usage and sale” was spot checked. According with the SOP recovered solvents should be used in the same process stage or same production line as appropriate and recovered solvent from one product should not be used for other product.

The SOP “Handling of returned finished goods” was spot checked.

3.14 COMPLAINTS AND RECALLS

Complaints

The SOPs describing the procedure for product recall and complaints investigations were available and were spot checked.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Not checked during this inspection.

PART 4: CONCLUSION

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, APIs (Pyrazinamide APIMF078, Isoniazid APIMF086, Artemether APIMF120 and Lumefantrine APIMF121) manufactured at Calyx Chemicals & Pharmaceuticals Ltd. Unit I and Unit II (Plant I, II, III, IV, V, VI & VIII), located at N-102, 91&90, MIDC, Tarapur, 401 506 District Palghar, Maharashtra, 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.