

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**
Finished Product Manufacturer
Part 1: General information

Name of Manufacturer	Quality Chemical Industries Ltd. (QCIL) (c/o Cipla Ltd.)
Unit number	No specific unit number specified.
Production Block	Only 1 production block at the specified address
Physical address	Plot 1-7 Luzira Industrial Park, P.O BOX 34871, Kampala, Uganda
Contact address	Mr. Emmanuel Katongole (ceo@qcil.co.ug), Chief Executive Officer, Quality Chemical Industries Ltd. Mr. Atul Vadepali (atulv@qcil.co.ug), Quality Assurance Manager, Quality Chemical Industries Ltd.
Date of inspection	3 – 5 September 2012
Type of inspection	Routine
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	HA, MA
Summary of the activities performed by the manufacturer	Production, quality control, packaging

Part 2: Summary

General information about the company and site

QCIL was established in 2007. QCIL is a joint venture company of Quality Chemical Ltd, Uganda and Cipla Ltd., India.

QCIL obtained a manufacturing License from National Drug Authority (NDA) in 2008 and commenced production of anti-retrovirals and anti-malarials in February 2009.

QCIL is a manufacturer in partnership with Cipla Ltd., India. The site is located at Luzira Industrial park about 2 km from Luzira city and about 10 km from Kampala.

History of WHO and/or regulatory agency inspections

The last official WHO inspection of the site was performed from 25 to 28 January 2010. The site was found to be compliant. Based on the facts that the company showed a satisfactory level of compliance during the last inspection, and that the overall performance reflects the quality associated with Cipla, the inspection was reduced to 3 days rather than 4.

Focus of the inspection

The inspection focused on the production and control of anti-HIV and antimalarial products. 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

The company opened with their presentation, which covered both commercial and technical aspects of the operation. The Site master file was confirmed as accurate.

CAPA Review: The CAPA's generated from the last inspection have been satisfactorily addressed.

Inspectors then reviewed the following documents:

- Product quality reviews
- Change controls
- Deviations
- Out of specifications
- Complaints
- Recalls
- Technology transfer
- Cleaning validation
- Maintenance programme and reports (the example of maintenance of AHUs was seen)

This was followed by an inspection of the quarantined raw material warehouse , approved raw material ware house and receiving area located on the 1st floor.

On Day 2, Inspectors visited the packaging components warehouse and the released raw material warehouse. More aspects of the quality system were also assessed.

Production was inspected. This included a visit of the dispensary, wet granulation and fluid bed drying, compression and compression tooling, in process quality controls, coating and packaging.

On Day 3, inspectors focussed on quality control, which included the wet chemistry laboratory, microbiology as well as stability chambers.

2.1 QUALITY ASSURANCE

Product quality review

Product quality reviews were performed as per the applicable SOP. A review period was set at one year after the first batch manufactured after the previous review had been completed.

Nevimune Tablets 200mg was chosen as an example.

API, excipients and packing materials used were properly documented with test reports available.

There were no deviations and or changes from documented procedures for prequalified products, as the processes were reportedly trouble free for the time period in question.

There have been no complaints or recalls affecting any of the WHO Prequalified products being manufactured at this site.

The product quality review gave no critical or major matters of concern.

Returns and rejects

The returns and rejects were performed as per the applicable SOP and were adequately handled overall.

Deviations

Deviations were managed in accordance with the applicable SOP.

Both planned and unplanned deviations were covered

No matters of concern regarding deviations were noted.

Technology transfer

This was reviewed in the context of the transfer of manufacturing of prequalified products from other Cipla sites located in India to Quality Chemicals.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general, it was found that all manufacturing processes were clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.

Most of the elements of GMP were considered to be adequately fulfilled.

2.3 SANITATION AND HYGIENE

A high level of sanitation and hygiene was found in every aspect.

2.4 QUALIFICATION AND VALIDATION

Process validation: Validation was reviewed for batches of selected WHO products which were recently transferred to the Uganda QCIL site.

Cleaning validation: the protocol for cleaning validation was reviewed for a fluid bed dryer and was considered to be adequate. A cleaning validation report was reviewed for the Neocota coater.

Qualification of stability chambers: Temperature mapping of the stability chamber at $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$ was reviewed. 8 probes were used for routine monitoring and were individually monitored by electronic means. Stability chambers were linked to an alarm in case temperature and humidity limits would exceed acceptable values.

2.5 COMPLAINTS

According to the procedure for complaints, complaints were logged upon receipt with a number and then the investigation would begin. Complaints were classified as “export” or “local”.

2.6 PRODUCT RECALLS

The SOP for recalls was reviewed and contained the necessary elements. Mock recalls were done to an acceptable level which covered verification of reconciliation of the quarantined batches from the distribution centers.

2.7 CONTRACT PRODUCTION AND ANALYSIS

This area was not inspected as production and analysis of prequalified products was not subcontracted by Quality Chemicals to other sites

2.8 SELF INSPECTION AND QUALITY AUDIT

No issues of concern were noted in this area.

2.9 PERSONNEL

For all aspects that were seen, there was an adequate number of personnel with the necessary qualifications and practical experience. All of the necessary elements were fulfilled.

2.10 TRAINING

The staff interviewed during the inspection was well trained and knowledgeable in their areas of work. Adequate GMP training had been given to staff and continuous training programs were in place.

2.11 PERSONAL HYGIENE

This area was found to be acceptable overall.

2.12 PREMISES

Storage areas

-Raw materials warehouse:

The raw material warehouse was located on the 1st.floor of a three-storey building. Access was via a stairway to a change room and thence over a step over barrier after donning overshoes, bonnets and gowns.

Photo depiction of the change procedure was clearly displayed on the wall. IPA hand spray was mandatory prior to entry into the warehouse and other manufacturing areas. Entry to all areas was via keypad and interlocking doors. Throughout the inspection several spot challenges on the interlocking system were made but there were no failures.

Toilets and washroom facilities for staff were segregated from the changing room and were in an excellent state of cleanliness and maintenance.

The warehouse was adequately lit, well ventilated and adequately maintained. Temperature and RH measurement were monitored with calibrated sensors. Department employees and QA regularly monitored air pressure differentials. The reporting procedure and remedial action for OOS pressure differentials was described in the applicable SOP.

Records of pest control and temperature mapping were not reviewed during this inspection.

The cold store temperature was continually monitored and alarmed for excursions. A sample of Tenofovir API was selected for later scrutiny of the analytical test results.

Raw materials were dispensed on this floor and transported by lift to the 2nd floor manufacturing areas. Entry to the room housing the LAF sampling booth was via an air lock. Materials entered through a separate pass box. When in operation, the pressure differentials for the LAF booth primary and HEPA filters were within the specified limits.

SOPs for managing the area were found to be adequate overall.

-Packaging components warehouse:

Packaging components were sampled under a separate LAF cabinet. When in operation, pressure differentials across both primary and HEPA filters were within set limits.

The balance used for weighing Aluminium foil was regularly calibrated. Cleaning was managed as per the applicable SOP.

Printed packaging materials were stored under lock and key.
Components and raw materials were selected for a later review of test records.

Label returns followed the applicable SOP, which addressed the removal of any overprinted batch numbers before replacing reels under lock and key.

Maintenance

Buildings maintenance, mechanical and electrical installations were covered by the applicable SOP. Pre-programmed maintenance was followed by another SOP. An annual schedule was generated as per the SOP which provided guidance on frequency and timing. Most maintenance was carried out on Sunday when there were no conflicting interests with production. A slippage time of + 2 days was built into the schedule.

A tablet compression machine, the compressed air generator and the AHU units servicing the compression area were chosen as examples. All servicing was completed with the time frame.

Servicing reports for various pieces of equipment were reviewed. In general, no matters of concern were noted.

2.13 EQUIPMENT

The SOP on maintenance was acceptable overall. No significant matters of concern were noted.

2.14 MATERIALS

The receipt of goods and labelling was verified to be adequate.

Status control and inventory control was found to be adequate as well.

Materials were issued on a first-in, first-out basis with batches being run to exhaustion before a fresh batch is issued as per the applicable SOP.

Material issued for a subsequently cancelled batch was returned to stores and recorded.

Spot checks on material holdings showed the written record to match the quantity actually present in the unopened containers and the part used container.

Sampling was found to be adequate overall.

2.15 DOCUMENTATION

The applicable SOP contained detailed instructions on the preparation and control of SOP's and the position within the organisation of who is responsible for writing, checking and authorising them.

QA kept records of review dates and expected relevant departments to adhere to the schedule and report any necessary amendments.

Updated issues displayed the edition number and the effective date. Old copies were replaced completely by the revised editions. Withdrawals and revision histories were recorded.

No matters of concern were noted.

Batch Numbering System:

Batch numbering was adequately managed as per the applicable SOP. A logbook of batches made augmented the SOP.

The date when mixing and blending commenced was used to calculate the expiry date.

Once a batch number is issued, it stays with the relevant batch and is never used again even if production is cancelled or discontinued in mid process.

Several documents were reviewed throughout the inspection. No matters of concern were noted with regards to the quality, completeness and accuracy of the documentation presented.

2.16 GOOD PRACTICES IN PRODUCTION

The production areas were situated on an upper floor and were accessed by a stairway. A second pair of overshoes and a hood were donned over the clothing worn in the warehouse. Entry was again via a step over barrier with an IPA hand rinse before entry into the corridor. Entry into processing area required additional wearing of overalls and bootees.

In general and throughout the process, all rooms involved in the various stages of manufacture were clearly labelled. All equipment lying idle or ready for use appeared visually scrupulously clean with appropriate status labels attached.

Dispensary

The dispensary housed a LAF booth. The room pressure differential with respect to the corridor and cabinet filter differential pressures were within the ranges specified. Cleaning records were satisfactory and followed the appropriate SOP. The balances were regularly checked with calibrated weights traceable to the national reference standard.

No matters of concern were noted.

Wet granulation

The batch manufacturing record (BMR) for one of the products of interest to PQ, was used to assess the processing stages.

Fluid bed granulation, milling and sieving

Details were recorded in the BMRs. The equipment seen was in an acceptable state of maintenance and cleanliness.

Batch reconciliation was recorded at this stage and results outside of the set limits would be investigated.

After blending of the sub lots, the batch is transferred to the bins and held in a staging area to await release for compression after assays for satisfactory uniformity of content.

Compression

Compression equipment was inspected with reference to batch records for the batch being processed at the time. No matters of concern were noted.

Coating

The coater was not in use at the time of the inspection but according to the descriptions given, coating solutions were made in a separate area adjacent to the coating room. Cleanliness and cleaning procedures were verified.

Packaging

The primary blister packing stations were inspected. Pressure differentials and airflow were verified relative to their design.

Blistering machine set up and component checks were verified. QA check that the setting of the batch number and expiry date is correct before authorising commencement of the packing run. Correct filling of the blister pockets was continually checked on line by a camera system. The system was checked by deliberate removal of a tablet from the blister prior to the camera position which caused rejection of the sealed strip.

The packing record was comprehensive and did not give rise to any matters of concern.

All secondary operations were recorded on the packing record and no matters of concern were noted.

Blister strips were regularly taken for leak testing. The conventional vacuum/methylene blue tracer procedure was used. Testing was performed in accordance with the applicable SOP.

Sampling consisted of 4 blisters every 4 hours or when there is any stoppage and start of machine. If the test failed, the activity was stopped and supplementary testing was performed as per the applicable SOP.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Testing of Components

Samples are taken using BS 6001 part 1 as a guide to sample numbers. Samples are subject to critical, major and minor AQL assessments.

All test records examined were satisfactory.

The Aluminium foil was tested for pin holes using a planar surface illuminator.

The specifications for the tests performed on the blistering foil for Lumartem (artemether+lumefantrine tablets) were reviewed and were considered to be satisfactory.

The dimensions measuring instrument used was calibrated.

An analytical report, preparation records and chromatograms were reviewed for assay of a PQ product. Adequate verification was performed prior to commencing an analysis, including primary verification injections (called pre-runs). Integration was baseline to baseline and performed automatically.

Microbiology:

Validation of the media, garment, petri dishes and glassware autoclave, was reviewed. 3 cycles were done to validate the distribution of heat in the empty chamber, 3 cycles were performed to confirm the heat distribution In the loaded chamber, heat penetration in media/ garment and accessory loads.

The temperature mapping records were reviewed for incubators. Hot spot and cold spot was identified. Temperature was monitored at the hot spot.

Media preparation records and master culture details and traceability to the sub cultures were reviewed. Only 2 vials were available at M4 from the master culture. Master cultures were on average reordered every 2 years.

Inoculation was performed in a laminar air flow cabinet which was claimed as Class 100 in a class 10,000 background. There were 2 airlocks leading to these areas, the 2nd of which was also claimed as class 10,000.

Pharmaceutical grade water is regularly sampled and tested. The 23 user points in the loop are tested at least once a month and every two weeks at the start and finish of the loop. Water was drained for 3 minutes prior to use as per instructions seen in production at each user point.

Sampling was done in accordance with the applicable SOP. Both plate counts and membrane filtration test procedures were employed. The trends for the past year were verified and showed acceptable results over time. No matters of concern were noted.

Wet Chemistry and Instrumentation

Sample control was managed by following the applicable SOP. All samples received were ascribed an AR number. This was entered into a register together with a full description, which includes a batch ID number.

Samples are distributed to technicians who have undergone competence training for the test in question.

The training record of an analyst in QC was reviewed. The record was comprehensive and detailed.

No matters of concern were noted

The in-house test procedures for lactose monohydrate USP35 were identical with the USP publication. No errors of transcription were noted.

The analytical report for a randomly selected batch of Tenofovir API was satisfactory.

The HPLC used in the assay has a reporting integrator without the capability to calculate results. Peak area manually transcribed to an Excel spread sheet with an inbuilt calculation. The cells containing the formula were password protected.

Stability testing

The programme was briefly reviewed using Duovir tablets as an example. Samples are tested at the conventional time intervals.

Results for the 30°C/75% RH condition from zero to 6 months showed no excessive degradation with impurities still within specification.

The stability chambers (30°/65% RH, 40°C./75% RH, 25°C/60% RH, 30°C/75% RH) were briefly inspected and contained sufficient space for the stability studies to be performed. Relative humidity and temperature monitoring was digitally performed on a continuous basis in 8 different areas of each stability chamber covering cold and hot spots. The number of tablets loaded and withdrawn was adequately documented and reconciliation was verified.

No matters of concern were noted.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, *Cipla Ltd, c/o Quality Chemicals Uganda Ltd. (QCIL), Plot 1-7, Luzira Industrial Park, Kampala, Uganda* was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

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