

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

Name of Manufacturer	Matrix Laboratories (Xiamen) Ltd
Unit number	NA
Production Block	Workshop: 1, 3, 4 & 7
Physical address	No 6, Yang tai Road, Xinyang Industrial Park –Haicang District Xiamen, Fujian Province, China 361022
Contact person and email address.	Ms. Ruth Lu ruth.lu@matrixlabschina.com Mr. Polavarapu Surendra Kumar kumar.surendra@matrixlabschina.com
Date of inspection	19 to 22 March 2012
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Zidovudine (APIMF179) Nevirapine (APIMF180)
Summary of the activities performed by the manufacturer	Production, packaging and quality control of various APIs

Part 2: Summary

General information about the company and site

Matrix Laboratories (Xiamen) Ltd. is engaged in the manufacturing of Active Pharmaceutical Ingredients (APIs), Intermediates and finished dosage forms (Tablets, Capsules and Granules). The site is located about 30KM from Xiamen International Airport. The site is constructed on a 10.5 acre plot and the main production blocks are built in an area of 57000M². There are seven API and intermediate manufacturing blocks with a break down as follows: one FDF block, three Warehouses, QC, QA, R&D, ETP, Engineering, Production Department, Utility building, Canteen building and Office building.

According to the company's presentation, the site started operation in 1997. Xiamen Mchem Laboratories was merged with Matrix (India) group in the year 2006, and renamed to Matrix Laboratories (Xiamen) Ltd in the year 2009. The site employed 446 employees.

History of WHO and/or regulatory agency inspections

This is the second WHO inspection on this site. The site had been inspected jointly by the EDQM and WHO in December 2009 and found to be non-compliant. In addition, the site had been inspected by the SFDA and renewed manufacturing licence and GMP license in 2011 for APIs, Intermediates and Finished Products.

Focus of the inspection

The inspection focused on the production and control of Zidovudine and Nevirapine 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

- Quality Management
- Personnel
- Buildings and Facilities
- Process Equipment
- Documentation and Records
- Materials Management
- Production and In-Process Controls
- Packaging and Identification Labeling of APIs and Intermediates
- Storage and Distribution
- Laboratory Controls
- Validation
- Change Control
- Rejection and Reuse of Materials
- Complaints and Recalls

2.1 QUALITY MANAGEMENT

In general, quality management system was in place and effectively implemented. For example, there was a system in place to handle change controls, deviation management, PQR, OOS etc. The necessary organizational structure, procedures, processes and resources were provided. Quality-related activities were defined, documented and recorded at the time they were performed. The Quality Department was independent of Production. The persons authorized to release intermediates and APIs were specified.

2.2 PERSONNEL

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

Personnel met during the inspection found experienced, knowledgeable, polite and prompt. It is recommended to provide more training and close supervision to minimize some of the common documentation errors.

2.3 BUILDINGS AND FACILITIES

Buildings and facilities used in the manufacture of intermediates and APIs were, in general, located, designed, and constructed to facilitate appropriate cleaning. They were designed to minimize potential contamination. In particular, dedicated blocks were available to manufacture APIs (Workshop 4, 1 and 7 for Stage I, II, III and drying for Nevirapine and Workshop 3 & 7 for Zidovudine). Adequate space was provided for the orderly placement of equipment and materials. The flow of materials and personnel through the building was designed to prevent mix-ups or contamination.

In general, building and facilities appeared satisfactory. In particular, block 7 found clean and tidy during the inspection. However, more attention should be given to block 4 and 1, in particular some of the equipment found rusty and not maintained appropriately at the time of inspection.

Utilities

Drawings for these utility systems were available. Overall, utilities were acceptable.

Water

Water used in the manufacture of APIs was suitable for its intended use. Appropriate specifications were established and monitored. The installation of the Purified Water System, and its validation and controls were acceptable.

Lighting

There were examples of inadequate lighting. (As per audit observation at Ware house storage area cloth curtains removed and CAPA implemented)

Sewage and refuse

Not inspected in detail. However, the ETP (effluent treatment Plant) appeared satisfactory.

Sanitation and maintenance

Written procedures were available for sanitation and maintenance of facilities and equipment.

2.4 PROCESS EQUIPMENT**Design and construction**

Equipment used in the manufacture of intermediates and APIs were generally of appropriate design, adequate size, and suitably located for its intended use. Production equipment was used within its qualified operating range.

Equipment maintenance and cleaning

Schedules and procedures were established for the preventive maintenance of equipment. Written procedures were established for cleaning of equipment.

Calibration

Control, weighing, measuring, monitoring and test equipment were calibrated according to written procedures and an established schedule. Records of these calibrations were maintained. The current calibration status of critical equipment was known and was verifiable.

2.5 DOCUMENTATION AND RECORDS**Documentation system and specifications**

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures. Production, control and distribution records were retained for at least one year after the expiry date of the batch. Specifications were established and documented for raw material, intermediates and finished API. Acceptance criteria was established and documented for in-process controls.

Equipment cleaning and use record

In general records of equipment use, cleaning, sanitization and maintenance were attached to equipment.

Records of raw materials, intermediates, API labeling and packaging materials

Records of raw material, intermediates, finished APIs, labelling and packaging materials were maintained.

Master production instructions

Master production instructions were available and were prepared, dated and signed by one person and independently checked, dated and signed by a person in Quality Assurance.

Batch production records

Batch production records were prepared for intermediates and finished APIs. Batch production records were numbered with a unique batch number, dated and signed when issued.

Laboratory control records

Laboratory control records included data derived from tests conducted to ensure compliance with established specifications and standards. Records were maintained for out-of-specification (OOS) investigations. Laboratory records were maintained in paper form.

Batch production record review

Written procedures were established and followed for the review and approval of batch production and laboratory control records. Deviation, investigation and OOS reports were reviewed as part of the batch record review before the batch was released.

2.6 MATERIALS MANAGEMENT

This area needed further attention. In particular, cloth curtain should be replaced. Materials should be stored at an appropriate places based on the storage condition applicable. It was recommended to pay more attention on the qualification of vendors, in particular KSM.

General controls

Written procedures were available describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials. A system was in place for evaluating the suppliers of critical materials. In the warehouse, materials were managed manually.

Receipt and quarantine

Upon receipt, each container of materials was examined visually for correct labeling, damage to containers, broken seals and evidence of tampering or contamination. Materials were held under quarantine until they were sampled, tested and released for use.

Sampling and testing of incoming production materials

Containers from which samples were withdrawn were marked to indicate that a sample has been taken.

Storage

Materials stored in fiber drums, bags or boxes were stored off the floor. Rejected materials were identified. For raw materials, a locked "Reject" room was available.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

In general, the processing status of major units of equipment was indicated.

In-process sampling and controls

In-process controls were carried out in the production facilities.

Blending batches of intermediates or APIs

Not inspected.

In general, production and IPC found adequate. Nonetheless, it is required to look into the existing cleaning of equipment and instruments procedure and amend accordingly. There should be a clear distinction be made on the cleaning status based on suitable study.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Manual Finished product labels must be changed to printed ones. More space should be provided for adequate packaging of finished products. Special attention should also be paid on dust extraction system etc.

Packaging materials

Not inspected in detail. Packaging materials were stored in a side room of the Raw Materials Warehouse and appeared to be adequate.

Label issuance and control

Not inspected.

Packaging and labeling operations

Packaging and labelling operations were not carried out during the inspection.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Facilities were available for the storage of all materials.

Distribution procedures

APIs were released for sale after QA approval.

2.10 LABORATORY CONTROLS

In general, laboratory was operating at an acceptable level of GLP compliance.

QC had adequate laboratory facilities. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data

were available. Specifications were established for Nevirapine and Zidovudine APIs. OOS results obtained were investigated and documented according to a procedure.

Reagents, HPLC Mobile phases and standard solutions were properly labeled. Those inspected were within usage date.

Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were certified by the application of appropriate tests to ensure standardization. Reference standards were properly labelled and stored. Working standards were dispensed in 14 amber vials for use within 12 months. Temperature in the reference standards storage fridge was monitored.

Testing of intermediates and APIs

Laboratory tests were performed for all intermediates. Instrumentation and facilities were adequate to conduct the tests required. Impurity profiles describing the identified and unidentified impurities were established for Nevirapine and Zidovudine APIs.

Certificates of analysis

Certificates of analysis (CoA) were issued for each batch of API. The re-test date was provided on the label and certificate of analysis. Certificates were dated and signed by authorized personnel from the QC and QA.

Stability monitoring of APIs

A written programme for ongoing stability determination was developed and implemented. Stability and on-going stability samples were stored properly. Temperature in the chambers was continuously monitored. Chambers were equipped with an alarm system.

Expiry and retest dating

Supporting stability information was available for expiry date assigned.

Reserve/retention samples

Appropriately identified reserve samples of each batch of Nevirapine and Zidovudine, reserve samples were stored in the same packaging system in which the Nevirapine and Zidovudine APIs were stored. Retention samples were stored under appropriate conditions.

2.11 VALIDATION

Validation policy

The company's overall validation policy was documented in VMP.

Validation documentation

A written validation protocol specifying critical processes steps and acceptance criteria was established.

Qualification

Appropriate qualification of critical equipment and ancillary systems were carried out.

Process validation programme

Critical process parameters were controlled and monitored during process validation studies.

Cleaning validation

Not inspected.

Validation of analytical methods

Not inspected.

2.12 CHANGE CONTROL

A formal change control system was established. Deficiencies were observed in the implementation of the Change Control Procedure.

2.13 REJECTION AND RE-USE OF MATERIALS**Rejection**

Intermediates and APIs failing to meet established specifications were rejected.

Reprocessing

Reprocessing was carried out in accordance with written procedures.

Reworking

Reworking was carried out in accordance with written procedures.

Recovery of materials and solvents

Recovery of materials and solvents was carried out in accordance with written procedure.

Returns

Not inspected.

2.14 COMPLAINTS AND RECALLS

Quality-related complaints were recorded and investigated according to a written procedure. Records of complaints were retained. The written procedure to recall products from the market was reviewed. The authorized person responsible for the execution and coordination of recalls was designated. No mock recall was performed so far.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

It was confirmed that no manufacturing activity was contracted out. It was noted that some of the analytical tests were contracted out to outside laboratories.

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, *Matrix Laboratories (Xiamen) Ltd, China* was considered to be operating at an acceptable level of compliance with WHO GMP guidelines 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.