



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

Part 1: General information

Name of Manufacturer	Matrix Laboratories limited
Unit number	Unit 1
Production Block	API production blocks MB01, MB02, MB03, MB04, MB06, MB07 and MB08
Physical address	Survey N° 10, Gaddapotharam, Kazipally Industrial Area, 502 319 Medak District, India.
Contact person and email address.	Mr. Pallab De, Sr. Vice-President, Corporate Quality Assurance, Pallab.de@matrixlabsindia.com
Date of inspection	February 14 th - February 16 th , 2011
Type of inspection	Routine
Active Pharmaceutical Ingredient(s) included in the inspection	Lamivudine Lopinavir Zidovudine Nevirapine anhydrous Nevirapine hemihydrate
Summary of the activities performed by the manufacturer	Production, quality control, packaging, storage and distribution of APIs.



Part 2: Summary

General information about the company and site

Matrix Laboratories is a subsidiary company of Mylan Inc., USA. Matrix is engaged in the manufacture of active pharmaceutical ingredients (APIs), intermediates and finished dosage forms. There are about 11 units, located in different parts of India, such as Hyderabad, Vizianagaram, Paravada, Nasik, Mumbai and Aurangabad. Unit 1 was opened in 1989 and only manufactures APIs and intermediates. Neither high pharmacological activity substances nor highly sensitizing materials such as penicillin or cephalosporin are manufactured on the site.

History of WHO and/or regulatory agency inspections

The Matrix Unit 1 facility has been inspected once before by the WHO in 2006, FDA in 2007, AGES Austria in 2008. FDA and EDQM inspections have covered Unit 2, which is adjacent to Unit 1 and which is also used to store stability samples and testing of microbiology samples from Unit 1.

Focus of the inspection

The inspection focused on the production and control of 5 APIs. It is noted that efavirenz and tenofovir disoproxil fumarate are no longer manufactured at the Unit 1 site for use in WHO products, as recently notified by the company. Going ahead, the company will implement an optimized process of Tenofovir Disoproxil Fumarate at Unit 1 site and seek approval from the WHO PQ team for use in WHO products. The inspection covered all the sections of WHO GMP Guidelines for APIs, including:

- Quality Management
- Personnel
- Buildings and Facilities
- Process Equipment
- Documentation and Records
- Materials Management
- Production and In-Process Controls
- Packaging and Identification Labelling of APIs and Intermediates
- Storage and Distribution
- Laboratory Controls
- Validation
- Change Control
- Rejection and Reuse of Materials
- Complaints and Recalls
- Contract Manufacturers (including Laboratories)

Inspected Areas



Day 1

After introductions and a brief company presentation, inspectors reviewed the following documents:

- Product quality reviews (PQR) for lopinavir (2009 and 2010), nevirapine anhydrous and nevirapine hemihydrate (2010), zidovudine (2010), lamivudine (2010).
- Change control register and procedure No. SOP/CQA/GMP/012/01, effective date 02.09.09.
- Procedure for “Investigation of out-of-specification (OOS) results” No. SOP/CQA/GMP/011/03, effective 12.01.11.
- Reprocessing procedure No. SOP/QAD/GEN/023/02.
- Selected OOSs.
- Procedure for “Handling and investigation of deviation” No. SOP/CQA/GMP/001/01.
- Deviation log register for 2010.
- Procedure for “Internal Quality Audit” No. SOP/QAD/GEN/010/03.
- Internal Quality Audit Schedule for 2010/2011.

In the afternoon, inspectors proceeded to the visit of the storage warehouses for starting materials and finished APIs, as well as the solvent tank farm.

Day 2

After presentation of the observations from the previous day, inspectors proceeded to the visit of the following areas:

- Block MB01.
- Block MB02.
- Block MB04.
- Block MB06.
- Block MB07.
- Block MB08.
- Solvent recovery plant.

Inspectors also reviewed the following documents:

- Selected batch records for the APIs under review.
- Lopinavir distribution record for 2011.
- Reactor equipment log records.
- Purified water system testing.

Day 3

Inspectors visited the HVAC of blocks MB-01 and MB-02 and the quality control unit.

The visit of the quality control laboratory included a verification of the following elements:

- Logbooks for AR numbers.
- Performance verification of the balances.

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- HPLC analyzers raw electronic data for selected runs and audit settings as well as a recent audit trail, user access privileges.
- FTIR spectrophotometer and associated software. Electronic data and user access privileges.
- Calibration of the GC analyzers.
- Reference standard bank (both official and in-house working standards).
- Retention samples area.
- Records of preparation of mobile phases and of various samples.

The following documents were reviewed:

- Pressure differential mapping for the clean area of MB-02.
- Cleaning validation approach and reports.
- Procedure for “assigning the analytical report numbers”, No. SOP/QCD/GEN/001/04.
- Procedure for “Vendor evaluation and approval”, No. SOP/CQA/GMP/014/01 effective 05.07.10.
- Procedure for “recovery solvents management”, No. SOP/PDN/GEN/015/02, effective 01.01.11.
- Analytical reports for critical raw materials.
- LOP-I/033/11/U-1 in-process step for THP content
- Contracts for solvent recovery.
- Qualification report for a new supplier.
- SOP for vendor qualification and approval.
- Master batch records for final steps for lopinavir, zidovudine (recovered ethyl acetate is used in final step).
- Procedure for maintenance and cleaning of air handling system of manufacturing block, No. SOP/ENG/AHU/001/05.
- Procedure for “Performance Qualification of Air handling System” No. SOP/ENG/AHU/009/01.
- Protocol for performance qualification of air handling unit No. PQ/ENG/AHS/MB-II.
- Preventive maintenance schedule for plant equipment for the year 2011.
- Preventive maintenance record for fluid bed dryer (Monthly, Quaterly & Annual).
- Qualification report for FD-102.
- Qualification report for RE-301.
- Procedure entitled "Training of employees" No. SOP/CQA/GMP/018/01.
- Training curriculum for 2010/2011.
- General cleaning and cleaning validation approach.
- General Manager job description.
- Deputy- General Manager job description.
- Job description for the Senior Manager of Quality Control.
- Procedure for "release of finished product to market" No. SOP/DA/GEN/014/04.
- Procedure for "labeling of finished product" No. SOP/PDN/GEN/002/01.
- Protocol for validation of cleaning procedure of equipment proposed for use in the product Lamivudine stage III (SVL III).



- Protocol for validation of the analytical procedure that was used during cleaning validation.

2.1 QUALITY MANAGEMENT

The quality management system was effective overall. Minor issues raised regarding product quality reviews were corrected as per the company's proposed corrective and preventive actions (CAPAs).

2.2 PERSONNEL

The personnel interviewed were considered to be knowledgeable and competent. An organization chart and job descriptions were available. Responsibilities of key personnel were adequately defined. The amount of time allocated to some of the trainings which had been described in the program was sometimes not realistic (e.g., only 1 hour of training on the entire ICHQ7). This has now been addressed.

2.3 BUILDINGS AND FACILITIES

Buildings and facilities used were in good condition in general, except for some design issues regarding the washing bays. Some minor maintenance issues were noted regarding the solvent recovery system for which the company has proposed adequate corrective action.

2.4 PROCESS EQUIPMENT

Process equipment was generally well maintained and covered by a maintenance program and qualified.

2.5 DOCUMENTATION AND RECORDS

The documentation system was acceptable in general.

2.6 MATERIALS MANAGEMENT

General controls, receipt and quarantine, sampling and testing of incoming production materials, were acceptable overall.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations were conducted in accordance with master production documents. Time limits were generally respected and in-process sampling and controls were performed as per instructions.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES



Packaging materials were acceptable except that the procedure for their labelling or identification, when stored in the packaging areas of the inspected production blocks, was not being consistently followed. This issue was satisfactorily addressed by the company.

2.9 STORAGE AND DISTRIBUTION

Facilities were available for the storage of all materials under appropriate conditions.

2.10 LABORATORY CONTROLS

Laboratory controls were adequate in general except for identity testing by FTIR. The issues which had been noted for identity testing by IR were satisfactorily addressed by the company through software upgrades, revised SOPs and training.

2.11 VALIDATION

The approach used for validation of production processes and for validation of cleaning was considered to be acceptable overall.

2.12 CHANGE CONTROL

The documentation of change controls was found to be acceptable overall. The SOP for change control was revised further to inspection observations to adequately address the release of batches that are impacted by a particular change.

2.13 REJECTION AND RE-USE OF MATERIALS

Solvent recovery was being performed by the company. All issues which had been noted were satisfactorily addressed.

2.14 COMPLAINTS AND RECALLS

The documentation of complaints was considered to be acceptable. The procedure for recalls was acceptable but no recall had been performed up to date.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Contract laboratories were not covered during this inspection, as all of the QC testing was performed on site. Contract manufacturers were held by adequate written agreements.

Part 3: Conclusion



Based on the facilities inspected, the personnel 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 Unit I* was considered to be operating at an acceptable level of compliance with WHO GMP guidelines and in particular, WHO Good Manufacturing Practice Guide 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

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