



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Matrix Laboratories Limited
Unit number	Unit 8
Production Block	PB 9
Physical address	G. Chodavaram Village, Poosapatirega Mandal, Vizianagaram District - 535 204, Andhra Pradesh, India
Date of inspection	25 - 28 May 2009
Type of inspection	Routine
Dosage forms(s) included in the inspection	FPP
WHO product numbers covered by the inspection	HA411, HA429
Summary of the activities performed by the manufacturer	Production and control

Part 2: Summary

The manufacturing site of Matrix Laboratories, Unit 8 (production blocks 1 to 9) located in G. Chodavaram Village, Poosapatirega Mandal, in the Vizianagaram District (close to Visakhapatnam) in the State of Andhra Pradesh, India, was inspected by a WHO prequalification inspection team on 25 - 28 May 2009.

General information

Matrix Unit 8 is located approximately 55km north of Visakhapatnam. Construction of the facilities started in 1993 and the company has continued to expand, with the completion of production block 9 in 2009. Two new production blocks, PB10 and PB11, were under construction at the time of the inspection. Besides the production blocks, there is also an administrative block, warehouses and a quality control block. Approximately 519 people were employed on site, including 217 production, 22 QA and 62 QC employees. The factory worked 3 shifts a day, 7 days a week.

History of WHO and/or regulatory agencies inspections

Unit 8 had previously been inspected by WHO inspection teams in May 2005 (PB 2 and 3), in March 2007 (PB 4 and 6), in February 2008 (PB 1 and 2 - Nelfinavir mesylate) and in June 2008



(anti-retroviral APIs, general GMP). The USA FDA last inspected Matrix Unit 8 in the beginning of 2009.

Focus of the inspection

The inspection focused on the new production block 9.

Inspected Areas

A sample of applicable procedures, records and activities were inspected as follows:

DAY 1:

Opening meeting

- Introductions
- Attendance Record
- Confirmation of scope and standard
- Company overview:
 - Description of manufacturing and product range
 - Changes since last inspection and proposed changes.

Personnel

- Organization Chart
- Job description for key personnel
- Training

Quality Management

- Annual Product Review
- Complaints
- Process deviation control
- Change control
- Contract agreements
- Supplier approval
- Document Control

DAY 2:

Buildings and Facilities

- Design and construction
- Personnel and material flow
- Tour through new production block 9

Production

- Reaction
- Drying
- Blending
- Packaging
- Cleaning



HVAC

- Design & construction
- Operation and maintenance
- IQ/OQ
- Monitoring and testing

Process water

- Design & construction
- Operation and maintenance
- IQ/OQ
- Monitoring and testing

Preventive Maintenance

DAY 3:

Validation

- Validation Master Plan
- Process
- Cleaning
- Computer validation
- Equipment qualification

Batch Record review

DAY 4:

Warehouse(s)

- Storage – quarantine, release, reject
- Starting Materials
 - Receipt, handling and storage
 - Identification
 - Sampling
 - Dispensing
 - Status Control

Closing meeting (4.45pm)

I. QUALITY MANAGEMENT

The GMP systems, stipulated in ICH Q7, were implemented in the quality system of Matrix Laboratories Limited Unit 8. Procedures and records were available for most performed activities. The awareness for quality topics was clearly present. Observations made during the inspection were presented in the full inspection report.

Product quality reviews (PQR) were performed annually (for one calendar year) for all products. Responsibilities, contents and time limits for the preparation of the report were defined. The PQR



for a selected product under inspection was reviewed in detail during the inspection. All produced batches in 2008 were included in the review, but the report did not contain sufficient interpretation of the raw data. No documented trend analysis was performed, and stability data was not complete. Data for products, manufactured in different production blocks, were analyzed conjointly. No separate analysis was performed to demonstrate that the production process, newly established in production block 9, was comparably stable as the already established process. The PQR 2008 for another product was briefly inspected.

A procedure for the documentation and investigation of deviations was available. With regard to the size of the site and the volume of APIs manufactured, very few deviations were recorded. According to the statements of company's representatives, deviations were not always recorded as such, if they could be corrected within a short time (e.g. deviations in pressure cascades of HVAC systems). Several planned and unplanned deviations were detected during the inspection, which were not handled within the system for deviations.

The company's program for internal audits (self inspections) was not covered during the inspection.

II. PERSONNEL

Generally the standards with regard to the number of qualified staff, organization and job descriptions were still on an appropriate level, as stated in the last report. The organization charts were completed down to the level of the different production blocks. The link between all organizational charts was clarified in the corrective actions.

Training and assessment of training effectiveness were conducted and documented according to an SOP. Training records for employees (staff from production and quality control, initial and continuing training) were satisfactory.

In the change rooms and airlocks to the clean areas in production block 9 - no procedure for gowning was available. The sequence of the dressing procedure was not clearly described in the SOP. The changing procedure for personnel entering the sampling and dispensing areas in the raw materials warehouse was not sufficiently described. The gowning in these areas was different from the gowning in the finished API handling areas, and not sufficient for the manufacture of finished products and intermediates (e.g. no overstep bench, no protecting coat). Even for sampling and dispensing of materials for the production of APIs - the environmental conditions were such that personnel would not be able to work without contaminating the area through excessive sweating due to the heat and humidity. All of these were corrected by the company.

III. BUILDINGS AND FACILITIES

Building and facilities in production block 9 were, as far as covered during the inspection, suitable. In production areas there was sufficient space for handling of equipment and materials. For handling of APIs after the last purification step a clean room area with classification 100 000 was available. Material and personnel flows were defined and allowed a logical order of goods processing. Nevertheless, the plans with material and personal flow contained some ambiguity and errors.



In the clean room area environmental conditions were controlled and suitable. Minimal pressure differences between adjacent rooms were between 2 and 4 Pascal, which is lower than the WHO recommendation for manufacture of finished products (5 to 15 Pascal). A written rationale for choosing the pressure cascade pattern could not be provided. For monitoring of pressure cascades each room was measured individually against atmosphere. Due to this system, differential pressures between adjacent rooms were cumbersome to calculate individually in practice. Rooms for dispensing and sampling of raw materials were located in the raw material warehouse. The rooms were not appropriate for handling of raw materials to manufacture finished products or finished product intermediates. Temperature and humidity were not controlled, the clean zone was not sufficiently defined (e.g. personnel gowning, missing overstep bench) and the dispensing room was not satisfactorily clean, although indicated on the status label. All of these issues were corrected by the company.

IV. PROCESS EQUIPMENT

Process equipment in the new production block 9 was dedicated and used to manufacture two products. Like in the other production areas, process parameters were controlled manually. Qualification of reactors, of the zone for handling intermediates and of the micronizing area was not reviewed during the inspection. Status of equipment was indicated on labels, usage of equipment was recorded in log books.

A system was in place for the preventive maintenance of equipment. A schedule for preventive maintenance was available; records of performed work were retained. During the inspection a faucet was leaking, water was dripping on the floor (washing room clean area). The problem was solved with an order for the technical in-house service. Measuring devices were labelled with calibration date and status; documents about calibration were not reviewed in detail during the inspection.

The new system for the generation of compressed air in production block 9 was qualified according to GMP guidelines. The quality of compressed air was tested at the point of use in the micronizing area.

The water loop of production block 9 was built together with the loop for production block 8 in a subsystem (tank and loops). Qualification documentation was available for the extension of the water loop; documents about design, installation and system start were included. For complete hot water sanitization of the system (including feed line) an occasional flexible connection was implemented in the system. A thermometer in the return water loop allowed correct measurement of sanitization temperature.

V. DOCUMENTATION AND RECORDS

Procedures, reviewed during the inspection were in general carefully prepared, suitably detailed, authorized and represented the current status.

Several batch records of the manufacture of a selected product, including six validation batches, were reviewed in detail during the inspection. The validation batches showed several discrepancies within the batch records and in comparison with presence data of production personnel, which could not be explained by the company. The review of ten further batch records revealed only minor discrepancies. Mainly a check on a sieve was not recorded throughout all



records. In one case a negative outcome was not further investigated and no deviation was opened. These aspects were clarified subsequent to the inspection and corrective actions were taken.

VI. MATERIALS MANAGEMENT

Materials management was not checked in detail. As far as covered during the inspection, processes were not significantly changed since the last inspection.

VII. PRODUCTION AND IN-PROCESS CONTROLS

Production block 9 was covered during the inspection except areas for micronizing and handling of intermediates. Raw materials were sampled and dispensed in two centralized areas in the warehouse for solid raw materials.

Process equipment in PB9 was dedicated for the production of the two products. The single production steps with process parameters and in-process controls were generally well defined and recorded in the batch manufacturing record. The use of equipment was traceable through equipment identification in the batch records. During the inspection batch records for ongoing production were available *in situ*. In the new production block process parameters were controlled and recorded manually.

For dedicated equipment no cleaning validation was conducted. Cleaning processes for equipment were not covered in detail during the inspection (including checks for effectiveness of cleaning processes). Deficiencies listed in the full inspection report on cleaning validation were clarified subsequent to the inspection and corrective actions were taken.

VIII. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The inspection did not cover procedures for packing and labelling of materials in detail. During the plant tour in production block 9 some containers were noted with insufficient information on the labels (e.g. raw materials and utilities). This was corrected by the company.

IX. STORAGE AND DISTRIBUTION

Raw materials and APIs were stored in different warehouses under different ambient conditions. During the inspection - warehouses were covered. Conditions in the warehouse for solid raw materials were not controlled. During the inspection, the temperature in one warehouse was out of specification (failure of air conditioning system). APIs were stored in an environmentally controlled warehouse on two floors.

These aspects were clarified subsequent to the inspection and corrective actions were taken.

X. LABORATORY CONTROLS

The system for the handling of stability samples was discussed. Several associated documents reviewed were not clear or contradictory. Not all necessary stability samples were taken, according to the internal process (e.g. yearly sample, validation batch samples, no deviation



opened). One sample was not tested at the right time, due to a wrong entry in the test schedule. Tests of stability samples were not always performed within the specified time frame, yet, the company did not consider this as a deviation from its SOP.

The procedure for the preparation of composite samples (e.g. during the validation of the premix) was not sufficiently detailed.

These aspects were clarified subsequent to the inspection and corrective actions were taken.

XI. VALIDATION

The overall site policy for validation and qualification was described in a validation master plan. Equipment, utilities and processes were listed in a table with status and qualification / validation date. Not all utilities like nitrogen, compressed air, technical (black) steam and cooling systems, were included in the qualification status report. The list of process validations did not show all performed validations, but only the initial and the latest one.

The following qualification records for equipment in the new production block 9 were reviewed during inspection: HVAC system in the new clean room area A and extension of the water loop and compressed air plant for micronization. Records of the process validation for the product under inspection, change in batch size and transfer to the new production block 9, were checked. Data in the processing records of the validation batches were in some points in contradiction to other documents. Discrepancies could not be explained by the company.

These aspects were clarified subsequent to the inspection and corrective actions were taken.

XII. CHANGE CONTROL

The system for management of changes was described in a procedure. Requested changes were listed in a register, documents about approval and implementation of changes were achieved separately. The reviewed changes were in general sufficiently documented. Responsibilities were defined; decisions about further investigations and actions were recorded.

XIII. REJECTION AND RE-USE OF MATERIALS

Processes of approval and rejection of raw materials were not covered in detail during the inspection. No material was reprocessed or reworked since the last inspection according to the company.

XIV. COMPLAINTS AND RECALLS

The procedure for the handling of complaints was described in an SOP. Complaints were listed in a register; investigations were recorded in detailed files. The investigations reviewed during the inspection were complete and well documented.

The recall procedure was not covered by the inspection. Traceability of dispatched batches was ensured with data included in the batch record.



XV. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

During the inspection a contract for analysis of raw materials with a contracted laboratory was reviewed. The assignment of responsibilities for finished product release was not clear.

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, Matrix Laboratories Limited Unit 8 and production block 9, was considered to be operating at an acceptable level of compliance with ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients.

Part 4: References

1. *Quality Assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection.* World Health Organization, Geneva, 2007
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2. WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report.* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 3
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