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WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information

Name of Manufacturer	**Mylan (Former Matrix) Laboratories Ltd,**
Unit number	**Unit VIII**
Production Block	Unit VIII: Blocks: PB-1, PB-2, PB-3, PB-4, PB-5, PB-6, PB-8, PB-9, PB-10.
Physical address	Mylan (Former Matrix) Laboratories Ltd, Unit VIII, G. Chodavaram Village, Poosapatirega Mandal, Vizianagaram District - 535204, Andhara Pradesh, India
Contact person and email address.	**Mr. Pallab De,** Sr. Vice-President, Corporate Quality Assurance, *Matrix Laboratories Limited, Plot no. 564 / A / 22, Road no. 92, Jubilee Hills, Hyderabad - 500033, India.* *Tel: +91-40-30866410, Fax: +91-40-30866699* *Mobile: +91-8008001497* *Email: pallab.de@matrixlabsindia.com*
Dates of inspection	15 - 19 August 2011
Type of inspection	Routine Announced Inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Antiretroviral (HA: HIV/AIDS) Active Pharmaceutical Ingredients (9) and related Premixes (2).
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and release of Active Pharmaceutical Ingredients and related premixes.

Part 2: Summary

General information about the company and site

The site inspected was the **Mylan (Former Matrix) Laboratories Limited (Unit 8), G. Chodavaram Village, Poosapatirega Mandal, Vizianagaram District - 535204, Andhra Pradesh, India**, hereafter called **Matrix Unit 8**. According to the Site Master File Document No. SMF/VZM/008 (Addendum-II) effective 01.04.2011, M/s. Matrix Laboratories Limited has a corporate office located at Plot No.564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500033, Andhra Pradesh India and is **a subsidiary of Mylan Inc. USA**. Matrix has the following other facilities:

- APIs:
  - 2 units at Kazipally Industrial area Hyderabad (Units 1 and 2).
  - 1 unit in Jeedimeta Industrial area, Hyderabad, Andhra Pradesh (Unit 3).
  - 1 unit Pashmylaram Hyderabad, Andhra Pradesh (Unit 7).

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- 1 unit in G. Chodavaram, Vizianagaram, Andhra Pradesh (Unit 8).
- 1 unit in Pharmacity, Parwada Visakhapatnam, Andhra Pradesh (Unit 9).
- 1 unit in Taloja, Maharashtra (Unit 11).
- 1 unit in Xiamen, China.

- FPP:
  - 1 unit for OSDs in Sinnar near Nashik.
  - 1 unit in Aurangabad.

Matrix Unit 8 is located 55km from Visakhapatnam airport on the Chennai - Kolkata national highway, on a 276,028.50m^2 plot with a built up area of 189,449.18m^2. The facility was established in 1993 as Vera Laboratories and was acquired by Matrix in 2004 which was in turn acquired by Mylan in 2007. The first production blocks were constructed in 1995 but have grown to include 11 production blocks (total reactor volume: 1,073KL), two common Pharma areas, two solvent recovery plants, three raw material warehouses, three finished goods warehouses, one process development laboratory and one QC/QA unit.

The APIs facilities at Matrix Unit 8 are multiproduct blocks with pharma area (synthesis, purification and finishing). The Pharma area has clean rooms classified as class 100,000.

According to the company presentation and the SMF, the site employed a total of 822 people distributed as follows:

Department	**Staff**
o Production	437
o Quality Assurance (QA)	38
o Quality Control (QC)	89
o Warehouse	18
o Process Development Lab	09
o Maintenance, Electrical & Projects	62
o EHS	25
o HR and support services	27
o Work men	121
Total	**826**

History of WHO and/or regulatory agency inspections

According to the SMF and company presentation, the site was licensed by the Director, Drugs Control Administration of Government of Andhra Pradesh under licence No. 177/VN/AP/96/B/R and had been inspected and/or approved by the following:

- USFDA, Nov. 2002 (covered one API)
- EDQM, CEPs (covered 8 APIs).
- WHO-PQ, May 2005 (PB-2 and PB-3: covered 4 APIs).
- USFDA, May 2006 (covered 3 APIs).
- WHO-PQ, March 2007 (PB-4 and PB-6: General)
- Drug control authority of Andhra Pradesh, May 2007.
- MHLW, Japan, July 2007 (Site accreditation).
- AGES/PharmMed, March 2008.
- WHO-PQ, Feb. 2008 (PB-1 and PB-2: covered 1 API)

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- WHO-PQ, June 2008 (covered 8 APIs)
- USFDA, April 2009
- WHO-PQ, May 2009 (Covered 8 APIs and 1 Premix).
- PMDA-Japan, April 2009 (covered 1 API).
- EDQM, April 2010 (covered 1 API)
- KFDA, 2011

This was the sixth inspection by WHO-PQ; the previous inspections were in 2005, 2007, 2008(2) and 2009.

Focus of the inspection

The inspection focused on the production and control of ARV (HA) APIs (9) and premixes (2) as outlined above. The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients (ICHQ7), 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 and Complaints and Recalls.

Inspected Areas

Day One: 15 August 2011

On arrival, the inspectors introduced themselves and exchanged business cards with the key staff of the company. The inspectors explained the procedure for the WHO Prequalification Programme, the procedures and standards used for inspection and timelines for processing the report and company responses to the inspection observations. The tentative inspection plan was discussed and confirmed. The company made a presentation about the company and the site to be inspected. These presentations highlighted the company profile, the description of the site, a summary of manufacturing capacities, the site inspection history, status of implementation of CAPAs to the observations of the last inspection and changes since the last WHO inspection. A copy of the presentation was obtained and will be filed in the company file at WHO.

The major changes highlighted include the following:

1. Facility changes:
    a. Premix raw material storage, sampling and dispensing facility created.
    b. Production blocks PB-10 and PB-11 commissioned.
    c. New Pharma area for drying, powder processing and packaging commissioned.
    d. Purified water new loop commissioned to cater for PB-10, PB-11 and New Pharma area (MLL/U8/PWS-002) supplied from DM water tank ST-708 (10KL).
    e. Additional Solvent recovery plant (SRP-2) commissioned.
    f. Bulk solvent tank plant commissioned.
    g. Additional Raw material warehouse (RM WH-3) constructed.
    h. Additional QC building constructed.
    i. Additional Finished Storage area created in common Pharma building.
2. Process changes:
    a. Additional API starting material sources for two APIs.

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b. A DMF of one API withdrawn from WHO.
c. BPR of one API harmonized in line with other Matrix units (batches not executed since November 2006).
d. The packing profile of one API revised.
e. Additional API starting material sources for one API. Optimized and validated process of Form-I and Form-II of this API.
f. Validated the Premix process using the API from optimized process.
g. Batch scale up of one API in PB-10, added new API starting material sources and validated an optimized process.
h. BPR of one API harmonized in line with other Matrix units (batches not executed since November 2009).

It was clarified that water used at the site was sourced from 2 bore wells, transported in truck tankers and stored in 2 sump tanks:

- One sump tank supplied water to boilers.
- The other sump tank supplied:
    a. A sample tank of 20KL which supplied the water purification system.
    b. Water chillers, gardening, floor cleaning in intermediate workshop areas and washrooms (toilets) without any treatment.

It was stated purified water was used in cleaning all process equipment and floor cleaning in Pharma area.

The following areas were reviewed:

1. SOP on vendor evaluation and approval. It provided for addition of a vendor on a provisional vendor list based on analysis of 3 samples, evaluation of supplier filled questionnaire and performance evaluation by R&D. Such vendor only progressed to a permanent vendor list after a test commercial purchase, manufacture of 3 batches and audit of the supplier facilities. This was later clarified to be associated with approval by the relevant regulatory authority, where applicable.
    - The approved vendor list dated 30/07/2011.

2. Raw material stores (RM-1, RM-2 & RM-3) plus related material receiving, sampling, storage and dispensing procedures.
3. The effluent treatment area. Large heaps of solid residues had been accumulated around the ETP sump tanks and the tanks were full to capacity. It was stated that the accumulation was because the vendor for handling waste had not accepted waste for several months. Communications with the vendor about this subject were presented to the inspectors. Photographic evidence was later provided indicating that the waste had been cleared.

Day Two: 16 August 2011

Inspectors provided feedback on the observations of the first day and the company concurred without any more clarification or reactions.

The presentation and discussion of the current synthetic processes in line with those presented in the APIMF and related updates followed.

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The discussion indicated that the certain current BPRs were not comprehensive in certain aspects. A number of issues identified were discussed with the company and adequate CAPAs have been received.

The inspectors proceeded on a plant tour and inspection. A number of discrepancies were observed in relation with storage and labelling of potable equipment, nitrogen cylinders, recovered solvents hoses found adjacent to PB-5 in the open. Adequate CAPAs have been presented to address these issues.

The inspection of the tank farm for solvents and liquid starting materials followed and adequate CAPAs have been received to address the deficiencies noted.

Inspection of synthetic processes in PB-10 followed. The building and equipment were generally in good state of repair, although some deficiencies were observed.

Day Three: 17 August 2011*:*

Inspectors provided feedback on the observations of the previous day. The programme of the day was discussed and agreed upon.

Inspection of the following areas and activities followed:

- Change control to transfer NF-902 from PB-9 to PB-10 for a validation. It was closed on 30.06.2011 and the filter was returned to PB-9 and subsequently to another block
- Water purification and distribution system.
- Production activities in PB-9.
    - Critical process parameters.
    - Change control to introduce automatic/pneumatic valve controls.
    - Pressure gauges on some reactors, conversion tables and recording in BPR.
- Production activities in PB-9.
    - Evaluation of the drying process: BPR and validation report. Issues related to the sampling intervals and process controls were noted and the process had to be revalidated.
- Production activities in PB-6.
    - The pipework for one of the synthetic process for one of the APIs in focus was not in place. It was established that most of the pipework was installed at the beginning of each campaign and removed at the end of the campaign. The PID was reviewed and was found not to indicate all the pipes and/or their specifications to facilitate complete installation. Appropriate CAPA was submitted.
    - The log books indicated the batches that were used in the recent optimisation of the process.

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Day Four: 18 August 2011

Inspectors provided feedback on the observations of the previous day. The programme of the day was discussed and agreed upon. The company provided the certificate of the oil used to lubricate leaf filters in PB-9 (LF-901 and LF-902)

The inspection of the QC laboratory and review of related documents followed. It was established that there were two QC laboratories:

1) QC-1: for analysis of raw materials, in-process control samples and intermediates. Stability chambers and microbiology laboratory were also located here.
2) QC-2: for analysis of API and stability samples. This had been opened less than 2 months before the inspection.

- Orientation of QC laboratory 2:
  - Wet analysis; Instrumentation HPCL; Particle size analyser; GC room; Fridge for working standards; Mobile phase preparation room; Glassware washing room with washing machine and drying oven (40^0C and 70^0C); Documentation room; sample preparation room; Ovens room for LOD (Hot air and Vacuum).
- Although inspectors had been informed that the first floor of QC-2 was being set up to accommodate the process development laboratory, a visit revealed the following:
  a) One room under, the control of QA, full of documents which were placed on movable shelves in a way which could not facilitate easy retrieval; these have been adequately rearranged.
  b) Another room, under the control of production personnel, had a number of equipment log books and other production related records placed in black polythene. These were later handed over to QA who was responsible for archiving.
  c) A room with poorly stored new laboratory glassware mixed with old equipment parts which made the room dusty and untidy.
- Reviewed the SOP on batch numbering system. The format was as follows:
  - Production batches: COD-X/NNN/YY where COD = product code, X = stage of processing, NNN = sequential number and YY = last 2 digits of the year. If the batch is manufactured in more than one block under the same code, the serial number in the 1st block starts from 001 and in the 2nd block starts from 501.
  - Recovered, reprocessed or reworked batches: COD-XZZ/NNN/YY where ZZ may be RE = crop recoveries, $RP_{(N)}$ = reprocessed batch (with subscript N for the serial number of reprocessing process if there is more than 1), RW = reworked batch, CRUDE = crude collected from MLs or washing MLs or REDRY = re-dried materials.
  - Dispatch batches: COD/YYMMNNN(Z) where MM = number representing month and Z may be C = Compacted, m = micronized, M = Milled and P = Pulverised. It was noted that batch number of dispatch batches of materials received from other units was not different from those produced on site.
  - Recovered solvents: Product code-X/RS-Solvent code(W)/NNN/YY, where RS = Recovered solvent and W may be C = column distillation or OS = Outside.
- Electronic data was backed-up on CDs every 15th of the month and deleted from the hard disk.

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- Working standards are prepared from approved batch and standardised against primary standard. Each time, 13 vials of WS are prepared, one for each month of the year plus one spare vial.
- IR instrument, QC/ASSET/224:
    - Desiccant was in good order and changed monthly or before if colour changes.
    - Ratio of sample: KBR used was 1 - 2: 300 – 400.
    - KBR dried at 250^0C for 1 hour and kept in dry box.
    - Wavelength accuracy was checked using Polystyrene film, Current Lot No. 009-8158-00240, use before 31.12.2014.
    - New standards are scanned every day and after every 6 samples which are freshly prepared.
- IR data for selected batches and working standard used was reviewed.
- Reviewed analysis of a number of batches of APIs:
    - One was a reprocessed batch that was reanalysed and approved. The results of the entire batch tree were reviewed, including selected verification of electronic raw data:
        - An approved source of the APISM was used. All had been sampled, NIR on each container and IR on composite sample.
        - Acceptable CAPAs have been received on noted issues on control of pooling to make a composite sample, system suitability evaluation for chromatographic tests of starting materials and no use of bracketing standards.
    - A batch that failed, was reprocessed, reanalysed and approved. The results of all the batches in the batch tree were reviewed and no issues were noted.
    - Acceptable CAPAs have been received on noted issues on control of manual integration of chromatographic peaks.
- OOS investigation
    - SOP was reviewed.
    - Selected OOS investigation report was reviewed, no assignable cause was identified, the OOS was confirmed and the batch reprocessed. The reprocessed batch met the requirements.
- Calibration of the HPLC. The SOP described adequate calibration every 6 months.

Day Five: 19 August 2011

Inspectors provided feedback on the observations of the previous day.
The following aspects were inspected or reviewed:

- Common Pharma with 7 modules: 6 operational and 1 under installation:
    - Module 1: drying
    - Module 2: drying, VTD-CO3 and VTD-CO4 - inspected in detail.
    - Module 3: FBD – under installation
    - Module 4: Sifter SF-CO1 and Multi-Mill (MM-CO3), inspected in detail. Acceptable CAPAs have been received on noted issues on recording and log books for room temperature and relative humidity.
    - Module 5: Pulverizer
    - Module 6: Blender

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  - Module 7: Dispensing and packing
- Finished Goods Store above Common Pharma. Controlled at 27^0C/65%RH.
- SRP-1:
  - Dedicated drums for transfer of recovered solvents were used.
  - There were 5 multipurpose columns.
  - Temperature monitoring of the column distillation process: 5 probes. (Still, Vapour, Column-bottom, Column-middle, Column-top)
  - Reviewed the recovery of Toluene, THF and Isopropyl acetate by column distillation.
  - Cleaning of the reactors and columns, SOP provided for batch to batch, periodic and product change over cleaning. Acceptable CAPAs have been received on noted issues on details and clarity of the SOP.
  - Solvents were recovered and reused at intermediate stages of processes. This was appropriately recorded in the BPRs of the batches reviewed.
  - Issues of a mix up in the designation of process as either reprocessing or rework have been resolved.
- PB-5:
  - Acceptable CAPAs have been received on noted issues on airlocks into the pharma area on the first floor, operating pressure limits for a Micron Filter, cleaning procedures for a multipurpose centrifuge and water used in the washing area.
- PB-2:
  - Recently upgraded and had airlocks/change rooms.
  - Acceptable CAPAs have been received on noted issues on storage of portable equipment, location for Multi-Mill MM-202 for intermediates, maintenance and cleaning of TD-202.
- PB-1:
  - Drying room for Premixes.
  - Common packing area; Acceptable CAPAs have been received on noted issues with the cleaning procedure.
- Review of the attendance of selected production and QC staff in the biometric database and quarterly reviews performed by the company. Review of the attendance of selected supervisors from two days before the inspection and throughout the days of inspection.
- Review of the CCTV camera recordings for the main gate:
  - Day recording (07.00 to 19.00) for 2 days before the inspection.
  - Evening and night recordings starting from 19.00 for the days of inspection.
- PQR:
  - SOP on Annual Product Quality Review (APQR) was reviewed. All intermediates and APIs were covered. The reviews followed a standard format. It provided for calculation of Cpk if data contained more than 20 batches and any Cpk < 1 had to be justified.
  - PQR for 2010 for selected APIs were reviewed.
    - Acceptable CAPAs have been received on issues noted.
- SOP on "Handling and Investigation of Deviations" was reviewed. This was a revised version of the SOP, the previous version not detailing a formal close-out.

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- SOP "Training of Employees". All departments were covered. During induction, new employees are provided with individual copies of ICH Q7. Heads of departments identified individual training needs. Approval was from QA and implementation by HRD. A training curriculum was drawn up with reference to specific SOPs. Of note was the absence in any training or refresher training in ICH Q7 in 2011. A module, TM/REF/CQA/07/003, dated 23/11/07 was available for ICH Q7. A QA employee was interviewed about ICH Q7 clauses and was not confident in the replies. This employee's formal training in ICH Q7 was in May 2010. Acceptable CAPAs have been received on noted issues on the Company's implementation of training and assessment of the effectiveness of training.
- An example of Validation was described in "Protocol for Performance of Purified Water Storage and Distribution for Production Blocks PB10, PB11 and Common Pharma". This covered the two loops, one for PB10 and the other for PB11 and Common Pharma. The sampling valves on the returns of the loops were identified. Phase 1 was conducted from 21/10/10 to 19/11/10, Phase II from 21/11/10 to 20/12/10 and Phase III from 21/12/10 to 20/12/11. Data was available for Phase I, Phase II and for the first 6 months of Phase III. Microbiological results on samples obtained from the sampling points, referred to above, were satisfactory. The Change Control, raised at the initiation of the work, was scheduled to be closed after the final review after the Phase III is completed.

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feedback and wrap up for the inspection and received reactions from the management of the company. There was consensus on all the observations made.

2.1 QUALITY MANAGEMENT

Generally quality management procedures were well executed. There was a documentation system at the site to support quality management and quality assurance. There was a Quality Unit consisting of Quality Assurance, Quality Control and Laboratory Quality Assurance. The responsibilities of the quality and production units were defined indication that the Quality Unit was independent from production.

There was a system for product quality review which covered all intermediates and APIs. Although the review was generally comprehensive, there were no recommendations for CAPAs to address the observed trends or out of trends.

There were procedures for handling deviations and change control although issues were noted with the initiation and approval of some changes.

2.2 PERSONNEL

Individual personnel responsibilities were defined in the organisation charts and individual job descriptions. Although the site generally had adequate numbers of personnel to carry out the tasks, it was noted that a substantial number of tasks were conducted by contract

personnel who were not under full control of the company. Furthermore, indications were that more numbers were needed in certain areas like engineering and maintenance.

Entry to critical production, storage and quality control areas was restricted to authorized personnel who underwent appropriate gowning.

There was a training programme and all departments were covered. During induction, new employees were provided with individual copies of ICH Q7. Heads of departments identified individual training needs. Approval was from QA and implementation by HRD. A training curriculum was drawn up with reference to specific SOPs. Of note was the absence in any training or refresher training in ICH Q7 in 2011.

Personnel interviewed records checked and operations observed indicated that more training and transfer of knowledge from R&D/Process development and corporate QA to operational level QA and production personnel was required to ensure that production would consistently be carried out in accordance to the designed processes and applicable GMP. For example, it was noted that production personnel were not conversant with synthetic procedures, and although the SOP for Change Control and associated documentation was satisfactory, the implementation was erratic and not understood. Acceptable CAPAs have been received on issues noted.

2.3 BUILDINGS AND FACILITIES

The building and facilities were designed to facilitate logical flow of production activities, although some pharma areas lacked airlocks to adequately segregate them from intermediate areas. Lighting in some sections of the workshop was constantly tripping and needed to be improved.

Buildings were constructed of painted, rendered masonry. Internal finishes were suitable for the activities conducted. Floors were of sealed concrete in warehouses; those in the production plants for intermediates were tiled. Walls and ceilings were painted. In the powder processing/"pharma" areas, finishes were of epoxy coated floors, with coved joints to walls. In the pharma areas, classification was to Class 100,000. The clean areas for purification stage were separate from those for the synthesis stages. The surfaces were generally smooth and the areas were supplied with separate AHUs. The HVAC system was well designed but its routine maintenance needed further strengthening.

Materials in Raw Material warehouses were stored on pallets on proprietary painted steel racking. Drummed solvents were stored similarly.

Rooms were allocated for sampling and dispensing. QC personnel were responsible for sampling. There were concerns regarding the containment of materials during these operations.

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There were two tank farms with tanks of $40M^3$ mild steel in bunded enclosures. The installation also included automatic sprinkler systems. Standards of installation and maintenance were generally good but some issues were noted.

The facility for bulk storage of Hydrochloric Acid was poor but a new installation was being constructed.

Water was purchased from outside, delivered in tankers and stored in underground sump before some was treated to different levels appropriate to its use. An extension to the Purified Water system had been installed in RB10, PB11 and the Common Pharma Area. The validation was reviewed and found adequate. The Purified Water System generally was satisfactory. Acceptable CAPAs have been received on noted issues on maintenance of a tank for brine solution for chillers and water stored in an inadequately covered and maintained underground sump and pumped to production workshops without further treatment.

Other utilities like steam, bulk nitrogen were generally good. A fire hydrant system was installed around the site.

Acceptable CAPAs have been received on noted accumulation of huge amounts of solid waste found packed in bags and heaped around the ETP. It was claimed that the contractor for waste management had not accepted waste for quite some time due to problems with his land fill.

2.4 PROCESS EQUIPMENT

Reactors were either of stainless steel or glassed lined steel, with overheads to allow to usual range of organic reactions requiring distillation/reflux from atmospheric pressure to full vacuum. Materials of construction were suitable. As required, nitrogen was available to provide inert atmospheres.

Gauges inspected at random were all seen to be within calibration date. Similarly, balances were correct of correct range and regularly calibrated.

Standards of installation and maintenance were generally satisfactory and acceptable CAPAs have been received on noted issues on cleaning of air inlet air grilles in pharma areas, cleanliness of some centrifuges, unusual odour from sifters and maintenance several pieces of equipment.

2.5 DOCUMENTATION AND RECORDS

The documentation system at the site included SOPs, manufacturing procedures, log books, testing procedures, records, specifications and related documentation, approaches and policies. These were designed, approved and controlled according to an established SOP. There were several concerns relating to documentation and document archiving practices but acceptable CAPAs have been received on the noted issues.

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2.6 MATERIALS MANAGEMENT

Materials were sourced from approved suppliers. On receipt, they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. The status labelling of some raw materials needed to be improved especially with respect sampling status. The storage of starting materials, intermediates and finished APIs was generally adequate and the storage conditions were regularly monitored.

Materials at different manufacturing stages were identified with a unique batch number and stage of processing. The hold times, retest dates and expiry dates of the different materials had been established and were being respected.

The control of materials was reviewed, starting with receipt of raw materials to dispatch of final product. Acceptable CAPAs have been received on noted observations on materials codes of API starting materials and processing of change controls related to changes in sources of API starting materials.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production processes were guided by documented procedures and instructions. Some production processes were conducted on campaign basis in multipurpose workshops and equipment. There were in-process controls conducted at appropriate stages to monitor the processes plus the quality of the intermediates and APIs. The cleaning procedures, design of the buildings, equipment and the planning of production facilitated prevention of cross-contamination.

In-process control samples were taken by production and submitted to QC. Details were entered into the BPRs as required. Some BPRs were reviewed *in situ* during the inspection. Details were observed to be entered correctly. Those BPRs reviewed were up-to-date.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Materials at different stages processing were identified with a unique batch numbers and stage of processing. Intermediates and finished APIs were packed using packaging materials meeting the relevant specifications. The labelling of finished API’s was adequately controlled.

The control over packaging was satisfactory.
"Approved" (green) labels were under the control of QC and final product labels were under the control of QA. SOPs, records and the security of labels were satisfactory.

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2.9 STORAGE AND DISTRIBUTION

Matrix Unit 8 had appropriate and separate storage areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. The packaging could support adequate storage and transportation and records maintained could support traceability.

Never-the-less, some observations were made on the storage of Raw Materials.

2.10 LABORATORY CONTROLS

There were two QC laboratories, QC1 and QC2. The latter was a new installation. Equipment available was adequate for the work required. All tests were conducted on-site, with the exception of XRPD (X-ray powder diffraction), used for polymorph determination, which was conducted at a Matrix corporate R&D unit in Hyderabad.

Stability studies were conducted by QC, following ICH requirements for long term accelerated and intermediate conditions. Out of range alarms were installed on each chamber and a print out of hourly readings taken.

The controls of both primary and working reference standards were satisfactory overall but there were some observations noted.

The control of Retained Samples was according to SOP, "Preparation and Control of Retained Samples for APIs and API Key Starting Materials". The Retained Sample store had been temperature-mapped with the hot spot identified and used as the point to monitor the room. Records were kept.

Instrument logbooks were maintained and that for Agilent 1200 HPLC system, QC/ASSET/130 was reviewed. Maintenance records for all HPLC systems were filed together. A logbook was used for the use of HPLC columns. When not being used, columns were stored in a dedicated cupboard.

2.11 VALIDATION

There was a system for qualification of equipment and systems and validation of process and procedures. Randomly selected equipment indicated that the equipment was validated. Utility systems had been qualified and were regularly monitored and requalified.

According to summaries in APQRs and selected reports reviewed, manufacturing processes and cleaning procedures related to the APIs in focus had been validated.

The validation data for the drying process of one Premix indicated that it required approximately 120 hours drying the premix to reduce the solvent content to less than 530ppm, but in normal production all the batches evaluated achieved the limit in 24hours - 48 hours

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(only next sampling point). This showed that the current practices were not justified by validation data.
The extension of the Purified Water storage and distribution system to production Blocks PB10, PB11 and Common Pharma was associated with appropriate qualification and validation of the system.

2.12 CHANGE CONTROL

Change Control was handled according to an approved SOP. All aspects that could affect the product quality and quality systems were covered with no exceptions. Explicitly stated was the requirement to raise a Change Control, using a CRAF form, before any changes could be made. Comments and observations were made on this enforcement related training.

2.13 REJECTION AND RE-USE OF MATERIALS

Materials and solvents were recovered either on-line within the workshop, in dedicated solvent recovery plants (SRP-1 and SRP-2) or at contract sites.
Recovered materials and solvents were reused at intermediate stages of the processes. Materials were also either reprocessed or reworked following approved procedures. The recovery process was guided by approved BPRs and the recovered materials were controlled by appropriate specifications. Selected examples were reviewed with minor observations. Clarity on the definition of these terms was needed.

2.14 COMPLAINTS AND RECALLS

Complaints were handled according to an approved SOP: "Handling of Customer Complaints". The logbook followed the required format, FM099/CQAGMP019/01. Examples inspected were satisfactory.

Recalls were handled according to an approved SOP. The Company had never had to instigate a recall. No mock recalls were conducted.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

XRPD studies were conducted by a Matrix R&D unit. Minor issues 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, **Mylan (Former Matrix) Laboratories Limited (Unit 8), G. Chodavaram Village, Poosapatirega Mandal, Vizianagaram District - 535204, Andhra Pradesh, India,** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines and in particular, WHO Good Manufacturing Practice for Active Pharmaceutical Ingredients.

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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.