

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

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|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Name of Manufacturer                                                 | Saurav Chemicals Limited                                                                             |
| Unit number                                                          | Site 2                                                                                               |
| Production Block                                                     | Pharma-II                                                                                            |
| Physical address                                                     | Bhagwanpura, Derabassi – Barwala road<br>Derabassi- 140507, Mohali District<br>Punjab,<br>INDIA      |
| Contact person and email address.                                    | Mr.Rajesh Kaushik<br>Head-Quality<br>Saurav Chemicals Ltd<br>Email:rajeshkaushik@sauravchemicals.com |
| Date of inspection                                                   | 16 to 19 July 2013                                                                                   |
| Type of inspection                                                   | Routine inspection (New site)                                                                        |
| Active Pharmaceutical<br>Ingredient(s) included in the<br>inspection | Neglected Tropical Disease API: Diethylcarbamazine<br>Citrate (APIMF 216)                            |
| Summary of the activities<br>performed by the manufacturer           | Production and quality control of APIs                                                               |

## **Part 2: Summary**

### ***General information about the company and site***

Saurav Chemicals Limited has two manufacturing sites. The first unit to manufacture pharmaceutical intermediates was set up at Saidpura, Derabassi in 1997, the second unit for API manufacturing was established at Bhagwanpura, Derabassi in 2004. At the time of the inspection the company had 486 employees as total, among which, 332 are at Derabassi site. This site located in the industrial area which is 20 km away from Chandigarh-

Diethylcarbamazine Citrate (DEC) API production was started in 2011 as claimed by the company.

There were five Pharma blocks on the site. Pharm II and pressure vessel block were used in the process to manufacture DEC. Pharma V included administration, QA and QC.

### ***History of WHO and/or regulatory agency inspections***

This was the first WHO inspection to this site. It had been inspected by the Danish Medicine Agency in 2007, Cologne Germany in 2011. This API was covered by the inspection of Berlin Germany in August 2012.

### ***Focus of the inspection***

The inspection covered all the sections of the WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

The inspection focused on the production and control of the Diethylcarbamazine Citrate (DEC) API. The products manufactured in Pharma II block included production of other APIs and was not dedicated to Diethylcarbamazine Citrate.

### ***Inspected Areas***

Production (technical areas and final processing areas of Pharma II).

Pressure vessel block

Water system and HAVC

Documentation, including SOPs and Batch Manufacturing Records (BMRs)

Quality control laboratory including microbiology laboratory

Warehouses

### **The following documents were reviewed but not limited as below:**

Day 1

- Organogram
- SOP-Job descriptions

- Analyst qualification
- SOP on SOPs
- Training SOP, training schedule 2013 with example
- APR SOP & APR for 2011 and 2012
- SOP for internal audit & related documents
- Query response APIMF
- Vendor qualification SOP
- Specifications for product release and STP for DEC
- Vendor approval list
- Batch Numbering system

## Day 2

- Process flow
- Change control, SOP and log with examples
- Deviation SOP and log with example
- Stability protocol and stability study summary data sheets
- STP comparison with stability specifications

## Day 3

- Validation master plan
- Process validation
- Drying validation
- PDR and technology transfer documents
- SOP for FG sampling
- Cleaning validation
- SOP for dedusting (RM & PM)
- Calibration for plant and QC related instruments SOP and annual schedule
- SOP on Preventive Maintenance & annual schedule 2013 with Example
- SOP on Re-working & Re-processing

## Day 4

- DI water spec & SOP with trend
- Vendor qualification SOP & related document
- Market Complaint SOP, logbook with example
- Quality Risk management SOP
- Document Archiving Procedure SOP
- CF018 Qualification
- Filled BPCR & FG data (for 3 validation batches)
- Product recall SOP
- Product return SOP
- Finished Product release documents
- OOS SOP with Logbook

- Working standard qualification SOP and log books
- Column maintenance SOP and log books
- Stability study data
- Key starting material DECC Specifications and STP
- Managing Password for users SOP
- Computer System Backup SOP
- Infra-Red Spectroscopy - instrument and Potassium Bromide pellets.

## **2. QUALITY MANAGEMENT**

The quality management system was generally well established, documented and implemented. The site organizational structure was presented and was acceptable. Quality-related activities were defined and documented in general. The Quality Assurance department was independent from production. The persons authorized to release APIs were specified.

### **Product quality review (PQR)**

The Annual Product Review 2011 and 2012 for DEC was reviewed.

Annual Product reviews were conducted with reference to SOP. Documents available for review covered 2011 and 2012. Only three production scale batches had been made, at the end of 2011. These were classified as Validation Batches.

The PQRs report that there were no OOS results, no complaints, no recall and no returns, no reprocessing or reworks,

### **Internal audits**

Internal Audits were conducted according to SOP. The report of the audit, conducted of production in March 2013 was reviewed and was compliant with the SOP.

### **Deviations**

Deviations had been recorded in the 2012 PQR for DEC. There was a planned deviation regarding a change in stability chamber. Documentation was acceptable.

## **3. PERSONNEL**

Key personnel responsibilities were specified in job descriptions. Job Descriptions were written according to “Job Responsibilities”, SOP.

The responsibilities of the following key personnel were reviewed:

- Quality Director
- QC Manager

- QC Executive
- Unit Head
- Pharma II Production Manager
- Pharma II Production Shift-in-Charge

The documents reviewed were generally comprehensive and acceptable.

## **Training**

Training was described in SOP. Training plan of 2013 and training record of QC analyst was inspected.

## **Personnel Hygiene**

The gowning and changing procedures when entering the clean areas were available for inspection.

## **4. BUILDINGS AND FACILITIES**

### **Design and construction**

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. In the Production Block, Pharma II, there was adequate space for the orderly placement of equipment to prevent mix-ups and contamination. However, the space of the warehouse was limited and not sufficient to accommodate the raw materials and finished APIs. The Inspectors understand that a construction programme is underway to improve warehousing space. QC areas and operations were separated from production areas.

### **Containment**

There were no other highly sensitizing materials either produced or handled at this site as far as the inspectors were aware, nor were there any other APIs of high pharmacological activity, such as steroids or cytotoxic as claimed by the management.

### **Utilities**

Utilities were available to provide the required range of temperatures for the activities being conducted. Vacuum and nitrogen were available as required.

### **HVAC**

Areas for the final processing and packaging of DEC were provided with filtered air to achieve a Grade D standard. The system, AHU system HVAC002, was of the

recirculation design with 10% fresh air intake. Air supply ducting was equipped with terminal HEPA filters.

### **Water**

The deionized (DI) water system was used in the manufacturing process and for cleaning the equipment. The raw water was from the on-site bore well.

The water system supplying DI water was adequate in general. At the time of the Inspection, a new system was being installed.

### **Lighting**

Adequate lighting was provided in Grade D areas and in technical areas.

### **Sewage and refuse**

Non-compliances observed during the inspection that was listed in the full report regarding drums status control in the area adjacent to the acids store were addressed by the manufacturer to a satisfactory level.

### **Sanitisation and maintenance**

The areas visited were clean and well maintained in general. The buildings were of painted, rendered masonry. Taking into account the construction work in progress, standards of housekeeping and maintenance were generally acceptable.

There were two maintenance workshops. One for general work appeared satisfactory although no work was being done.

## **5. PROCESS EQUIPMENT**

### **Design and construction**

The design and construction of reactors and other equipment related to the process was adequate for the activities being conducted. The product contact surfaces of the equipment were suitable for the processes being conducted.

### **Equipment maintenance and cleaning**

The manufacturing equipment within Pharma II 2 was inspected. A SOP "Cleaning of Equipment and Line Clearance" was available for inspection.

## **Calibration**

The calibration status of control, weighing, measuring, monitoring and test equipment was checked during the site inspection. Those items reviewed (pressure, temperature gauges, balances etc) were calibrated and in date.

## **Computerized systems**

No computer system was used in the production and control of the API except those used to particular analytical instruments e.g. HPLC.

## **6. DOCUMENTATION AND RECORDS**

### **Documentation system and specifications**

SOPs were controlled according to SOP "Preparation, Review, Approval, Revision, Distribution Control and Destruction of SOPs and Formats.

Initiation, change and withdrawal were conducted according to Change Control SOP. Superseded SOPs were withdrawn and logged on format "Document Distribution and Retrieval Record". All old copies were shredded and old master SOPs stamped "Superseded Copy" and archived for 7 years.

Materials specifications gave details of version numbers and references to previous versions.

### **Equipment cleaning and use record**

Equipment was not dedicated for the API inspected. Records of major equipment use and cleaning were showed in the BMR. Non-compliances observed during the inspection that was listed in the full report regarding the cleaning and inspection of the inner surface of the equipment were addressed by the manufacturer to a satisfactory level.

### **Master production instruction (master production and control records)**

Master production instructions were available for inspection.

### **Batch production records (batch production and control records)**

Batch production records were available and reviewed. As an example, a batch of final stage was reviewed with reference to the SOP "Approval and Release of Finished Product". The SOP included a checklist of requirements including the review of BPCRs of all stages, cleaning and analytical records of all stages, issuance of labels, correct closure of OOSs, deviations and the generation of Certificates of Analysis. The documents are retained in QA for 7 years.

## **Laboratory control records**

The maintenance of laboratory records was inspected. For electronic data from the chromatography instruments, details were described in SOP "Backup/Archival and Restoration of Analytical Data from Computer Systems". On a daily basis, data was transferred within the computer system of each instrument to a second internal hard drive. Details were recorded in a log "Record of Analytical Data Backup". The electronic raw data was removed from the computers every two months according to the company. The data was copied to CD, by the IT Department and retained in QA.

The SOP "Electronic Data Documentation" described aspects of access levels.

## **Batch production record review**

The BMR was available for review. The only batches made were validation batches at the time of inspection.

## **7. MATERIALS MANAGEMENT**

### **General controls**

Written procedures describing the receipt, quarantine, sampling, testing and approval or rejection of materials were available. The receiving materials were described in SOP "Receipt and Storage of all Incoming Raw Materials and Packing Materials". Non-compliances observed during the inspection that was listed in the full report regarding material management in one of the storage area were addressed by the manufacturer to a satisfactory level.

### **Vendor approval**

Vendor approval procedure was reviewed. Approved vendor lists for general raw materials, key raw materials and packaging materials were available. The supplier approval procedure and documents were inspected and considered to be acceptable in general.

### **Receipt and quarantine**

Receipt and quarantine of all materials was managed manually.

### **Sampling and testing of incoming production materials**

Starting and packaging materials were sampled according to a documented procedure. The containers sampled were labeled as such.

## **Rejects**

The Solids Warehouse had a dedicated, locked room for the storage of rejected raw materials. At the time of the inspection, this room was empty.

## **8. PRODUCTION AND IN-PROCESS CONTROLS**

### **Production operations**

The manufacturing facility and equipment for DEC located in Pharma II was not dedicated to this API. There was no DEC production being carried out during this inspection. Other API was under production. The production was organized in campaign based.

Raw materials were weighed and dispensed in the warehouse. Non-compliances observed during the inspection that was listed in the full report regarding conditions in the dispensing room, including the gowning procedure and dust control were addressed by the manufacturer to a satisfactory level.

## **9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

### **Packaging materials**

Packaging materials were received, quarantined and released according documented procedures and specifications.

### **Packaging and labeling operations**

After drying, the API was loaded directly into the containers in the drying room before the weight of each container, the inner bags sealed and labels applied.

Labels used on containers of intermediates or APIs indicated the product name, manufacturer name and address, batch number, manufacturing date and re-test date.

## **10. STORAGE AND DISTRIBUTION**

### **Warehousing procedures**

Facilities were provided for storage of raw materials, packaging materials and intermediates.

There were demarked areas for quarantine and released materials and a secure area for rejects.

## **Distribution procedures**

APIs and intermediates were released for distribution after they had been released by the Quality Unit according to the procedure.

## **11. LABORATORY CONTROLS**

### **General controls**

There was an independent Quality Unit. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available.

### **Testing of intermediates and APIs**

Testing was performed according to approved specifications, test methods and related SOPs.

### **Stability monitoring of APIs**

The QC department was responsible for stability testing of finished APIs. The stability samples were taken according to the defined program and stored in a long-term stability chamber with condition.30<sup>0</sup>C/75%RH

### **Expiry and retest dating**

The shelf life of the inspected API DEC was labeled 24 months. 18 months stability data was available at the time of the Inspection.

### **Reserve/retention samples**

Retention samples of each batch of API were kept in a temperature/RH controlled storage room.

### **Handling of out of specification (OOS) results**

The OOS/OOT handling procedure and log book was reviewed and acceptable in general.

## **12. VALIDATION**

### **Validation policy**

The validation master plan was reviewed and discussed.

## **Process validation**

The requirements for the validation of the DEC process were defined in protocols written for each stage, with corresponding reports summarizing the results. Due to time constraints, those documents relating to the first and last stages were reviewed. The drying steps of Stage III and Stage IV were the subject of separate documents and not included in the documents relating to the all the other steps of these stages.

Non-compliances observed during the inspection that was listed in the full report regarding process validation were addressed by the manufacturer to a satisfactory level.

## **Cleaning validation**

The equipment used for manufacturing DEC was not dedicated. Cleaning validation was reviewed and discussed with the company.

## **Qualification**

A centrifuge was chosen as an example for inspecting the Equipment Qualification documents. The relevant DQ, IQ, OQ and PQ documents were reviewed and considered to be acceptable in general.

## **13. CHANGE CONTROL**

Change control was managed according to SOP. The scope included changes that could impact on product quality. Changes were classified according to rules into three categories. The records for changes were reviewed.

## **14. REJECTION AND RE-USE OF MATERIALS**

### **Rejection**

Intermediates and APIs failing to meet established specifications were handled according to a documented OOS procedure.

### **Reprocessing**

According to the relevant SOP, when an OOS was confirmed a decision to reprocess (repeat a step in the BMR), or rework the material, was made on a case-by-case basis. There were only three validation batches made so far. The company stated that it had never been necessary to reprocess or rework on DEC and this was supported by the PQR.

## **Reworking**

Rework was possible in defined circumstances and covered by a documented procedure.

## **Recovery of materials and solvents**

Acetone and IPA recovery was carried out by online recycling and used in DEC manufacture. The 2<sup>nd</sup> crop recovered from mother liquor was recovered from stage III and combined into the third batch for final purification. This issue was discussed with company during inspection.

Specifications for fresh and recovered acetone were available and details were reviewed and no observation made. According to the BMR, both fresh and recovered acetone had to be used for the final processing stage.

## **Returns**

A procedure for return is available for inspection.

## **15. COMPLAINTS AND RECALLS**

No complaints relating to DEC had been received during 2012. Procedures for handling complaints and recalls were available. No recall of DEC API had been made.

## **16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

No manufacture or testing of DEC API was contracted out.

## **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, Diethylcarbamazine Citrate (APIMF 216) manufactured at Pharma-II, Site 2, Saurav Chemicals Limited, Bhagwanpura, Derabassi – Barwala road, Derabassi- 140507, Mohali District, Punjab, INDIA was considered to be manufactured in compliance with WHO GMP 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 2 years, provided that the outcome of any inspection conducted during this period is positive.