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Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Saurav Chemicals Limited
Corporate address of manufacturer	Saurav Chemicals Limited Plot No.370, Industrial Area, Phase-II, Panchkula, Haryana State; India, PIN-134 109
Inspected site	
Address of inspected manufacturing site if different from that given above	Vill.Bhagwanpur, Barwala road, Derabassi, District Sahibzada Ajit Singh Nagar, Punjab, INDIA - 140507
Unit / block / workshop number	Unit 3, Pharma-II
Manufacturing license number	1784-OSP, 1827-OSP for contract manufacturing activities
Inspection details	
Dates of inspection	25 to 28 April 2016
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs
General information about the company and site	Saurav Chemicals Limited is a joint venture company with Mitsubishi with three Units. The inspected site Unit 3 was located at Vill.Bhagwanpur, Barwala road, Derabassi, District Sahibzada Ajit Singh Nagar, Punjab, INDIA – 140507. It is in the industrial area about 20 km away from Chandigarh-Airport. The number of personnel employed by the site at the time of the inspection was 482. There were five production blocks in Unit 3. Among these blocks, Pharma II and pressure vessel block were used for manufacturing of Diethylcarbamazine Citrate (DEC) API. These blocks were not dedicated to DEC production. One manufacturing process was applied to DEC production. The finished DEC APIs were released with two specifications: USP and WHO grade (in house).

History	This was the second WHO inspection with previous inspection by the WHO performed in July 2013. The site had also been inspected by US FDA and Danish Medicine Agency in 2015.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text: Product quality review Quality risk management Deviation handling Change control Vendor approval Complaints and recalls Material management Technical agreement Lay out review Warehouse of solid materials Validation Master Plan Cleaning validation Equipment qualification Production MB-II Chemical area Production MB-II Clean area Reprocess, Reworking Blending operation Computer system validation Batch numbering system QC lab: Sample receiving and distribution HPLC Empower 3 access control and data management Analysis and data review Stability studies Retention sample handling OOS, OOT HAVC Water system Product release Finished goods warehouse Underground tank farm area.
Restrictions	No

Out of scope	No
WHO product numbers covered by the inspection	Diethylcarbamazine Citrate (APIMF 216) NTD (neglected tropical disease)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification

PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	**Brief summary of the findings and comments (where applicable)**

Brief summary of the findings and comments

1. Quality management

The quality management system was established, documented and implemented.

The site organizational structure was presented and was acceptable. Quality-related activities were defined and documented. The Quality assurance department was independent from production department. The persons authorized to release intermediates and APIs were specified.

Product quality review (PQR)
A SOP for PQR and PQR for Diethylcarbamazine Citrate of 2015 were reviewed. Stability study was performed under condition of 30^0C RH 75% and 40^0C RH 75%. There was no recall and no complaint reported. Change controls, deviations, OOT and OOS were reported and reviewed.

Review of quality and yield of Diethylcarbamazine Citrate (DEC) API was done by using Process Capability (Cp) as described in the procedure. DEC manufactured on the site was produced by one process only. There were two grades of DEC: USP and WHO grade. They were reviewed in the same PQR.

CAPAs
Annual Review of the adequacy of CAPAs was described in a SOP.

Quality Risk Management
Quality risk management and risk assessment was handled and performed according to a documented procedure. Various approaches to risk assessment were allowed, but the focus was on a quantitative FMEA model with descriptions of 3 levels for probability, severity and detectability, and RPN calculated from this. The risk assessment log book for 2015 and 2016 was available for review. One example risk assessment report regarding the change control of batch size increase was reviewed and discussed.

Deviations
Deviations were handled according to a SOP. Deviations in the 2015 PQR of Diethylcarbamazine Citrate were reviewed. The deviations listed were minor deviations and found acceptable generally.

Product release
Product release was handled according to a SOP. The release procedure and check list were reviewed. Release procedure after repackaging was reviewed.

2. Personnel

Personnel qualifications
There was an adequate number of personnel suitably qualified by education and training to perform and supervise the manufacture of APIs. The personnel met during the inspection were experienced and appeared to be knowledgeable about GMP.

An organization chart was available. Key personnel responsibilities were specified in job descriptions and a sample of these were selected for review and generally found acceptable.

Training
Training was not covered by the inspection.

Personnel Hygiene
Personnel hygiene requirements appeared acceptable as required. The requirements for entry into the Grade D cleanrooms were available. Staff observed in these areas wore appropriate protective clothing.

3. Buildings and facilities

Design and construction
The workshops for the production and packaging of Diethylcarbamazine Citrate API were not dedicated to this API but were generally located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture of the APIs.

Contamination during the final stages of production, including packaging, was minimized by these activities taking place in a suitably controlled Grade D environment.

Adequate space was provided for production and QC activities.
A new finished goods warehouse had been started in use since September 2013. Temperature was controlled and monitored below 25^0C. Temperature mapping of this finished goods warehouse was checked.

An underground tanks area was built since the last inspection. Tanks were installed and in use from 2015.

Utilities
A SOP for revalidation of HAVC system and testing reports were available and reviewed. Adequate ventilation, air filtration and exhaust systems were provided. The HVAC system provided filtered air to the Grade D cleanrooms. In general it was reviewed and generally found acceptable.

Deionised water
A SOP for deionised water monitoring was available. Deionised water specification and testing procedure were reviewed. Flow rate, temperature and conductivity were monitored on line. The system was sanitized monthly.

4. Process equipment

Design and construction
The equipment used to manufacture DEC API were not dedicated to specific steps of the manufacturing process. The equipment viewed appeared to be of suitable design and construction for the allocated process in general.

Equipment maintenance and cleaning
The equipment viewed during the inspection appeared to have been suitably maintained and in acceptable condition. Documented procedures and records were available for equipment preventive maintenance.

Cleaning procedures and records were available for equipment and those reviewed were satisfactory.

Computerized systems
ERP system was used for issuance of BMR. Empower 3 were used in the QC lab for networking of HPLC and GC. Non-compliances observed during the inspection that was listed in the full report regarding computerised system validation were addressed by the manufacturer to a satisfactory level.

5. Documentation and records

Documentation was controlled according to a documented procedure which was reviewed during the inspection. A system was in place for documentation management.

Equipment cleaning and use record
Equipment was cleaned according to written procedures. Cleaning records were maintained. Equipment log book for a glass line reactor was checked. Log books were kept and showed the usage of the equipment.

Master production instructions (master production and control records)
An approved master batch production control record was available for DEC APIs.

Batch numbering system, BMR issuing log and release log were reviewed and found acceptable.

6. Materials management

Suppliers of materials were required to be approved according to a SOP. Starting materials were categorized into three classes: key starting material (KSM), packaging material and general material. The approval process was described in the SOP. Suppliers of KSM and packaging material were required to be reevaluated periodically. Examples of suppliers audit report were reviewed.

Starting materials were received, quarantined and released according to company procedure. Sampling of starting materials was performed by QC personnel according to a documented sampling plan. Appropriate environmentally controlled sampling areas were available in the warehouses.

7. Production and in-process controls

The production of DEC was performed according to the instructions in the BMR. The steps reviewed indicated that the BMR had been kept up to date. Each major piece of equipment was appropriately labelled with a status label. Production of DEC was operated in the different manufacturing blocks.

Chemical area and clean area of Pharma II were inspected. DEC manufacturing operation was in processing at different stages.

Blending batches of intermediates or APIs
A SOP on blending of material was reviewed. Blending operation generally was not performed for finished DEC but could be allowed if there is reprocessed batch according to the blending procedure.

8. Packaging and identification labelling of APIs and intermediates

A brief inspection of the pharma II packaging area was undertaken. Packaging was not in operation at the time of inspection.

9. Storage and distribution

The company had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Manual records for stock and distribution were maintained.

The environmental conditions for the storage of DEC API were specified and appropriately monitored. Records of monitoring were maintained.

APIs were only released for distribution to third parties after they have been released by quality assurance.

10. Laboratory controls

General controls
The company had an organized and suitably equipped QC laboratory. Equipment included HPLCs, GCs and other testing instruments. HPLCs and GCs were networked and empower 3 was used.

Testing of intermediates and APIs
QC testing was conducted as specified in the relevant specification and according to documented test methods. The sample receiving and distribution log book was checked. Samples for testing were kept in a designated area.

Primary reference standards were available and working standards were standardized against the primary reference standards.

HPLC was used for testing of DEC API. The computer access control, authorization of the functions, as well as electronic data in HPLC was checked during the inspection.

Stability monitoring of APIs
A range of stability chambers were available. At least one batch of API per year was required to be placed on on-going stability study.

Reserve/retention samples
There was a designated temperature controlled area for storage of retention samples. A sample of each batch of API manufactured was kept. Retention samples were stored in container systems that comprised of the same materials as those used for the final API. Temperature and RH was controlled under specified conditions.

Handling of out of specification (OOS) results
A OOS/OOT handling procedure was reviewed. Microbiology OOS was managed by a separate procedure. There has been no microbiology OOS ever at the site.

11. Validation

Validation policy
The company's overall validation policy was described in a Validation Master Plan.

Process validation programme
A SOP described the procedure and requirement for process validation. Last process validation protocol and report of DEC were checked. Both fresh and recovered batches were included in the process validation.

Cleaning validation
Cleaning validation procedure was reviewed. Worst case approach was applied to cleaning validation in Pharma II.

Cleaning validation protocol and report reviewed was performed in 2016. The protocol specified that both swab and rinse method should be used. Acceptance criteria was specified after calculation. A glass line reactor was chosen as example equipment and the testing results were checked.

Validation of analytical methods

Recovery study method validation for cleaning validation was briefly reviewed. Protocol and report were available for inspection and found acceptable.

Equipment qualification
The procedure and requalification schedule of equipment were reviewed. Equipment was re-qualified periodically. A requalification checklist performed in April 2016 was reviewed.

Computer validation
Computer validation procedure was briefly reviewed. A SOP for electronic data documentation and a SOP for backup/archival and restoration of analytical data from computer system were presented for review.

12. Change control

There was a SOP for change control, verification of changes post implementation by QA was available in the form attached to the SOP. Change control log book of 2016 was checked during the inspection.

13. Rejection and re-use of materials

Reprocessing/reworking/recovery of finished APIs or intermediates was handled according to a SOP. The recovery of solvents and material were performed during process. They were reviewed during the inspection.

14. Complaints and recalls

Complaints were handled according to a documented procedure which was reviewed. It was the responsibility of QA to investigate complaints and instigate CAPA if necessary. A specified form was used to record complaints and their resolution. Complaints in 2015 were reviewed and discussed.

There has been no recall of this API since last inspection.

15. Contract manufacturers (including laboratories)

No manufacture or routine QC testing was contracted out. XRD testing was contracted to an external testing lab. The technical agreement was reviewed during the inspection.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned Diethylcarbamazine Citrate (APIMF 216) manufactured at Saurav Chemicals Limited located at Vill.Bhagwanpur, Barwala road, Derabassi, District Sahibzada Ajit Singh Nagar, Punjab, INDIA – 140507 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 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf