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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)

Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Andhra Organics Ltd
Corporate address of manufacturer	Plot No 8, SVCIE, I.D.A. Jeedimetla, Hyderabad – 500 055, Telangana, India
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Plot No 110A, IDA, Pydibhimavaram, Mandal Ranasthalam, District Srikakulam, Andhra Pradesh, India
Synthetic Block	PB-09, PB-10, PB-15, PB-16
Inspection details	
Dates of inspection	21-24 May 2019
Type of inspection	Initial inspection
Introduction	
Brief description of the manufacturing activities	There were 18 production buildings as well as several ancillary buildings housing utilities, quality control and assurance, storage and administration. The production buildings were dedicated to manufacture of respective intermediates and APIs. Production stages of Trimethoprim took place at the following buildings: PB-15: 3,5-dibromo-4-hydroxy-benzaldehyde (DBHA) PB-16: 3,4,5-trimethoxy-benzaldehyde (TMBA) PB-10:1-phenylamino-3-(3,4,5-trimethoxyphenyl methyl) acrylonitrile (PATA) PB-09: Trimethoprim API

General information about the company and site	Andhra Organics Ltd was established in 1999 and begun its manufacturing operations in 2001. In 2004, it became part of Virchow group of companies. The site is located approximately 80 Km from Visakhapatnam airport, in Pydibhimavaram, an industrial area, where several pharmaceutical manufacturers are established. Andhra Organics Ltd. is a separate legal entity with its own site management reporting to Virchow board of directors. Site quality head reports to head of corporate quality and regulatory affairs. Purchase, finance and R&D are shared between companies of the Virchow group.
History	This was the first WHO PQ inspection. The site is regularly inspected by CDSCO (July 2018) and Drugs Control Administration of Andhra Pradesh (February 2017). The site was also inspected by USFDA in October 2015 in the context of a key intermediate.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The following areas were inspected: Workshops, Utilities, Warehousing, Solvent Storage, Production Blocks, Analytical and Microbiological Laboratories explicitly used for the manufacture of Trimethoprim.
Restrictions	N/A
Out of scope	Parts of the site not concerned with the manufacture of Trimethoprim were not inspected.
WHO API or APIMF covered by the inspection	APIMF339 Trimethoprim
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices

HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	Summary of the findings and comments

1. Quality management

A formal documented system of quality assurance was established, with procedures covering all expected key quality elements being in place. QA and QC departments were independent of production. Site QA was reporting to head of corporate quality and regulatory affairs. Operations were specified in written form and GMP requirements were essentially being met. Procedures were in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Product and processes were monitored and these results considered during batch release. Regular monitoring and reviews of the quality of APIs were being conducted according to documented schedules and procedures. Batch release was performed according to an established procedure and QA was responsible for product release. It was noted that release was customer specific since QA would release partial quantity of a batch based on customer order. Hence release of a batch was carried out several times depending on customer orders. Following the inspection all observations were adequately addressed and appropriate CAPA were applied.

2. Personnel

There were approximately 470 full time staff working at the time of inspection, including 15 employees in QA, 59 employees in QC and 254 employees in production. In addition, there were approximately 300 contract employees performing supportive operations including warehousing activities. The site was operating 24 hours/day in 3 shifts. Personnel met during the inspection appeared to have knowledge of GMP principles and showed that they received initial and continuing training, including hygiene instructions, relevant to their responsibilities. The procedure on training was applicable to all employees involved in GMP activities. Induction training was conducted in six days and it included general HR topics, safety training and GMP training. Following satisfactory completion of the induction training programme, department specific training was provided. QA personnel was responsible for preparing an annual training programme based on feedback from department heads and for ensuring training sessions and evaluations were carried out and relevant records were maintained. Measures were taken to prevent unauthorized people from entering production and QC areas and appeared to be effective. An organization chart was available and reflected the reporting hierarchy. Job descriptions defining duties and responsibilities of key personnel were available. Responsibilities for production and QC/QA were well separated. There were eight QA persons qualified to perform batch release. Training records and job descriptions of two QA people were randomly selected for review.

3. Buildings and facilities

Production stages of Trimethoprim took place at the following buildings:
PB-15: 3,5-dibromo-4-hydroxy-benzaldehyde (DBHA)
PB-16: 3,4,5-trimethoxy-benzaldehyde (TMBA)
PB-10:1-phenylamino-3-(3,4,5-trimethoxyphenyl methyl) acrylonitrile (PATA)
PB-09: Trimethoprim API
In addition, there were several tank farms, recovery solvent areas, a solvent drum warehouse, a solid raw material warehouse, finished product warehouse, engineering stores and workshop as well as a fabrication shed and a scrap yard. It was noted that the fabrication shed was untidy with empty and in use gas cylinders lying on the floor and a rusty sheet metal roller exposed to weather conditions. In general, buildings where manufacturing took place were in good condition although the room in building PB-16 where the key starting material (intermediate) TMBA, was manufactured was located on the ground floor and was open to the outside environment. The main tank farm was not adequately maintained; corrosion and oxidation were observed on tank support bands, railings and ladders. In addition, concrete and metal pillars in the surrounding area, supporting pipes and electrical wiring were not appropriately maintained. Although solvent drums were stored on wooden pallets, no pest control measures were in place in the solvent drum warehouse. Some of these drums contained flammable solvents. Pest control was contacted to a third party and relevant procedures and records were discussed during the inspection. The final stages of Trimethoprim manufacturing were carried out in class 100,000 rooms in building PB-09. Environmental qualification of the clean areas was reviewed in detail during the inspection. A dedicated PW system was installed in PB-09. Analytical and microbiological laboratories were located on the second floor of the QA&QC building next to Building PB-09. Following the inspection all observations were adequately addressed and appropriate CAPA were applied.

4. Process equipment

Process equipment for the manufacture of DBHA, TMBA, PATA and Trimethoprim API were dedicated. Materials of product contact were suitable. Reactor systems, and utilities, were installed to allow reflux, distillation and cooling required to make the APIs of interest. Tools and equipment were uniquely identified, and status labels were generally used. Similarly measuring equipment were labelled including calibration status. In general, they were maintained according to written procedures and a plan for preventive maintenance was available.

5. Documentation and records

The documentation system was generally well established. Procedures on creating SOPs and document control were available. The issuance, revision, superseding and withdrawal of documents were controlled. However, a table with full revision history was not included in each procedure and documents. It was noted that several procedures had been newly introduced or revised 15 days before the inspection took place and their implementation could not be verified.

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures. Specifications were established for raw materials, intermediates and APIs. BMRs in general included sufficient instructions for each process stage and were retained for each batch processed. Batches were numbered according to a written procedure of product batch number. Labels were not always controlled and appropriately placed. Following the inspection all observations were adequately addressed and appropriate CAPA were applied.

6. Materials management

There were written procedures describing receipt, labelling, quarantine, storage, and handling of materials, as well as procedures for sampling, testing and approval or rejection of materials. Deficiencies were observed regarding the labelling of finished product containers. Following the inspection all observations were adequately addressed and appropriate CAPA were applied.

7. Production and in-process controls

In general, production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use. Calibration procedures and records for scales were presented. Standard weights and their certificates were available. Closed systems and dedicated pipes were used for material transfers from reactors to centrifuges. Examination of the flow of the manufacturing process and relevant equipment was in line with the BMRs examined during the inspection.

8. Packaging and identification labelling of APIs and intermediates

Intermediates were handled, as required, in dedicated containers. Examples were seen of those use for TMBA, 4-amino sulfonyl aniline and isoxamine. Hold times for intermediates were not established. An "Approved" label was affixed on finished product containers upon completion of analytical testing, but no release label or other indication was affixed on the containers after release. Following the inspection all observations were adequately addressed and appropriate CAPA were applied.

9. Storage and distribution

Raw Materials, Packaging Materials, Intermediates and Finished APIs were stored at different warehouses. A temperature-controlled area was available and temperature mapping had been carried out for the finished product warehouse.

10. Laboratory controls

The analytical laboratory was inspected. The premises were generally of an acceptable standard and well equipped. Four HPLCs, 3GCs, 1UV and 1IR spectrophotometers were installed and linked to a server using appropriate software. The server was located on site. Data was manually backed up every three days and monthly. Two copies were maintained by IT and QA. Access control was established, and roles were defined. Documents were organized in an appropriate manner and retrieval was achieved in a timely manner. Some raw material specifications were checked at random. A procedure on handling laboratory incidents was presented.

There was a dedicated area for the microbiology lab. This was generally well constructed. A procedure for entry and exit from the laboratory was available. Certificates for growth promotion media were presented as well as for microorganisms. The procedure on growth promotion was briefly reviewed. Logbooks for consumption were available. A procedure for neutralization of Trimethoprim was presented.

11. Validation

A Validation Mater Plan was available. Procedures for validation and qualification of equipment, systems, utilities, processes and analytical methods were in place. Initial qualification of the clean areas in PB-09 where Trimethoprim manufacture took place was carried out in 2014. The latest requalification which was carried out in 2018 was reviewed. AHUs 901, 902 and 903 were supplying filtered air in the clean areas. 85% recirculation was achieved.

12. Change control

A change management procedure was available. The procedure was applicable to all GMP related operations. QA was responsible for evaluating the initial change request, request feedback from involved departments, assess the impact and finally verify the effectiveness.

13. Rejection and re-use of materials

The company had in place procedures for recovery and usage of recovered solvents. It described batch numbering system and the operations relating to recovery of solvents based on their use on the same stage.

14. Complaints and recalls

The company had established procedures for handling complaints and recalls

15. Contract manufacturers (including laboratories)

Some discrepancies in relation to qualification and establishment of contracts with transport companies as well as with the company providing pest control services were identified. Following the inspection all observations were adequately addressed and appropriate CAPA were applied.

Part 3	Conclusion – Inspection outcome

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, ***Andhra Organics*** located at ***Plot No.110A, I.D.A, Pydibhimavaram (V), Ranasthalam (M), Srikakulam District - 532 409, Andhra Pradesh, India***, was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

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. ***Short name: WHO GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS 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-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 961, 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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
    Short name: WHO TRS 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. ***Short name: WHO TRS 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.
    Short name: WHO TRS 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.
    Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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 production 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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

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