## Part 1
### General information

#### Manufacturers Details

<table>
<thead>
<tr>
<th>Company information</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of manufacturer and address</td>
<td>Delta Finochem Pvt. Ltd Gate no. 350, Village Wadivarhe, Tal-Igatpuri dist-Nashik, 422 403 India</td>
</tr>
<tr>
<td></td>
<td>North latitude: 19.98º East longitude: 73.8º D-U-N-S: 91-844-4399</td>
</tr>
<tr>
<td>Manufacturing blocks</td>
<td>• Block A and Block A Clean Room • Block C • Block E</td>
</tr>
<tr>
<td>Corporate address of manufacturer</td>
<td>Plot No.: 121, M.I.D.C Area, Satpur, Nashik - 422007. Maharashtra, India</td>
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</tbody>
</table>

#### Inspected site

| Address of inspected manufacturing site if different from that given above | As above |
| Manufacturing license number | 25/NKD/92 & Form – 25 for manufacturing intermediates and APIs. |

### Inspection details

| Dates of inspection | 11 – 13 September 2017 |
| Type of inspection | Initial |

### Introduction

| Brief summary of the manufacturing activities | The manufacturer was involved in the manufacturing, packaging, labeling, testing and storage of intermediates APIs. |
| General information about the company and site | History of the company: • 1978 – Formation of Delta Industries • 1978–1994 – Manufacturing of Bromides & other Intermediates @ Plot # 121, MIDC- Satpur, Nasik • 1994 – Started Manufacturing of Phase Transfer Catalyst @ Plot # 121, MIDC-Satpur, Nasik • 2000 – Date of Incorporation of Delta Finochem P.Ltd |
• 2003 – Move to the New Facility at Wadivarhe (Gat # 350, Village Wadivarhe,Taluka-Igatpuri,Dist-Nasik) for Manufacturing of Phase Transfer Catalyst
• 2003 - Plot # 121, MIDC-Satpur, Nasik converted in to the Research Centre
• 2003~ 2004 – Started Manufacturing Intermediates
• 2006~2007 – Started Manufacturing API
• 2012 ~ 2013 – Received DSIR Certification of the Research Centre
• 2012 ~ 2013 – Received GMP Certification of Wadivarhe (Gat # 350, Village Wadivarhe,Taluka-Igatpuri,Dist-Nasik) unit.

Manufacturing Unit II was located at Gonde, about 5 kms from the Wadiwarhe Site. Unit 2 was used for distillation of Organic Bromides and Fine Chemicals.

### History

This was first WHO inspection

The site was inspected by the following authorities:

<table>
<thead>
<tr>
<th>Authority</th>
<th>Scope of inspection</th>
<th>Dates of inspection</th>
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</thead>
<tbody>
<tr>
<td>Central Drugs Standards Control Organization, India CDSCO</td>
<td>19/10/2012</td>
<td>GMP inspection</td>
</tr>
<tr>
<td>CDSCO</td>
<td>14/03/2013</td>
<td>GMP inspection</td>
</tr>
<tr>
<td>CDSCO</td>
<td>27/08/2013</td>
<td>GMP inspection</td>
</tr>
<tr>
<td>CDSCO</td>
<td>03/09/2015</td>
<td>GMP inspection</td>
</tr>
<tr>
<td>Maharstra, India FDA</td>
<td>27/10/2016</td>
<td>Vigilance visit</td>
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</tbody>
</table>

### Brief report of inspection activities undertaken

### Scope and limitations

- Pharmaceutical Quality System
- Documentation system
- Production System
- Facilities and Equipment System
- Laboratory Control System
- Packaging/labelling System

### Restrictions/out of scope

- Microbiological laboratory

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
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<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<tr>
<td>AQL</td>
<td>Acceptance quality limit</td>
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<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
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<tr>
<td>APQR</td>
<td>annual product quality review</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
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<tr>
<td>BDL</td>
<td>below detection limit</td>
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<td>BMR</td>
<td>batch manufacturing record</td>
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<td>BPR</td>
<td>batch packaging record</td>
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<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<tr>
<td>CC</td>
<td>change control</td>
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<td>CFU</td>
<td>colony-forming unit</td>
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<td>CoA</td>
<td>certificate of analysis</td>
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<td>CpK</td>
<td>process capability index</td>
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<tr>
<td>DQ</td>
<td>design qualification</td>
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<tr>
<td>EM</td>
<td>environmental monitoring</td>
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<tr>
<td>FAT</td>
<td>factory acceptance test</td>
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<td>FBD</td>
<td>fluid bed dryer</td>
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<td>FG</td>
<td>finished goods</td>
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<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<td>FPP</td>
<td>finished pharmaceutical product</td>
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<tr>
<td>FTA</td>
<td>fault tree analysis</td>
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<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<td>GC</td>
<td>gas chromatograph</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<td>ID</td>
<td>identity</td>
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<td>IR</td>
<td>infrared spectrophotometer</td>
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<td>IPC</td>
<td>In process control</td>
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<td>IQ</td>
<td>installation qualification</td>
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<td>KF</td>
<td>Karl Fisher</td>
</tr>
<tr>
<td>LAF</td>
<td>laminar air flow</td>
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<tr>
<td>LIMS</td>
<td>laboratory information management system</td>
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<tr>
<td>LoD</td>
<td>limit of detection</td>
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<tr>
<td>LOD</td>
<td>loss on drying</td>
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<td>MB</td>
<td>microbiology</td>
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<td>MBL</td>
<td>microbiology laboratory</td>
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<td>MF</td>
<td>master formulae</td>
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<tr>
<td>MR</td>
<td>management review</td>
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<td>NIR</td>
<td>near-infrared spectroscopy</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<td>NRA</td>
<td>national regulatory agency</td>
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<td>OQ</td>
<td>operational qualification</td>
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<td>PHA</td>
<td>preliminary hazard analysis</td>
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<td>PM</td>
<td>preventive maintenance</td>
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<td>PpK</td>
<td>process performance index</td>
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<tr>
<td>PQ</td>
<td>performance qualification</td>
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<tr>
<td>PQR</td>
<td>product quality review</td>
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</table>
Part 2 | Brief summary of the findings and comments (where applicable)

**Brief summary of the findings and comments**

1. **Pharmaceutical quality system**
   In general the system for managing quality encompassed the organizational structure, procedures and processes. There were QA and QC departments that were independent of production. In general deviations from established procedures were documented and explained. Procedure was in place for notifying management of regulatory inspections, serious GMP deficiencies, product defects and related actions.

   The traceability of records and documentation system were satisfactory.
Product Quality Review (PQR)

The SOP “Procedure for generation of annual product quality review (APQR)” was discussed. According to the SOP an APQR shall be prepared for a product having more than 5 batches during the year.

APQR covered but was not limited to:
- Number of intermediates and API batches manufactured
- Review of finished product dispatch details
- Review of critical in-process control and critical API test results
- Review of quality of batches
- Review of yield details
- Review of deviations, change controls, rejected materials
- Review of complaints
- Review of recalls, reprocessed and reworked batches
- Review of returned batches
- Review of CAPAs
- Review of stability and trends
- Review of critical raw materials vendors
- Review of OOS/OOT
- Review of validation packages

Environmental monitoring (EM) trends and purified water system trends were separate documents.

PQR was performed annually and according to the SOP should be completed by the end of February of the following year.

PQR of PRAZIQUANTEL for 2016 and 2015 were reviewed and discussed.

Quality risk management (QRM)

The SOP “Procedure for quality risk management” was discussed. According to the SOP QRM was applicable:
- Each stage of manufacturing process
- Inspection
- Packaging/distribution of products
- GMP system

Tool specified in the SOP for RM was:
- Failure modes and effects analysis (FMEA)
- Cause and effect diagrams
- FTA
- HACCP
- HAZOP
- PHA
- Risk ranking and filtering
As per company directives applied tools were FMEA, Ishikawa diagram and brain storming. Scoring from 1 to 5 was used for RPN calculations.

Management review (MR)
The SOP “Procedure for conducting management review meeting” was discussed. According to the SOP MR shall be comprised every six months. According to the SOP the following items should be covered by MR:

- Review of previous MR meeting minutes
- Review of non-conformities raised during system audit
- Review of customer satisfactory survey/feedback/complaints
- Review of process performance, product conformity
- Review of status of CAPA
- Review of Quality policy, objectives and their status
- Review of resources
- Review of training records
- Review of recommendations for improvements
- Any other issues

MR minutes were discussed.

Deviations
The SOP “Handling of deviations” its flow chart and register were discussed. Deviations were classified as:

- Critical
- Major
- Minor

Minor deviations were renamed “incidents” and were handled separately.

A system of “5 why’s” and Ishikawa diagram were applied for root cause investigations. QRM shall be applicable to critical deviations. Deviation registers were maintained product specific. Deviations should be closed within 30 working days.

A Deviation number and short explanation of the deviation was recorded in related batch processing record.

Corrective actions and preventive actions (CAPA)
The SOP “Procedure for corrective and preventive action” and register for 2017 were discussed. The SOP was applicable but not limited to:

- Deviations/non-conformances
- Complaints
- OOS
- Self-inspection/external audits
- APQR
- Regulatory issues
According to the SOP, CAPAs were proposed by each concerned department and evaluated by QA and closed within 45 working days. CAPA related to the unplanned deviation XX was discussed.

**Change control (CC)**
The SOP “Change control procedure” and registers for 2016 and 2017 were discussed. CCs were classified by QA department as:
- Minor
- Major
- Permanent
- Temporary

CC registers were maintained:
- Product wise
- General CC
- Document changes

Changes were initiated by each concerned department and approved by QA. Change Controls recorded in 2016, were reviewed and discussed.

**Self-inspection**
The SOP “Procedure for Self-inspection” was discussed. Self-inspections were performed by a cross functional team. According to the SOP all departments should be audited once in six months. Self-inspection schedule for 2016 and 2017 was presented to the inspectors. Cross checks showed that schedules were followed.

Self-inspection observations were classified as:
- Critical
- Major
- Minor

The Self-inspection team members’ qualification files were available.

Audits were performed following departments’ check lists. Shelf inspection check list for quality control department was discussed. CAPAs were submitted by the audited department and evaluated by QA. Follow-up was performed by QA.

**Data integrity**
The SOP “Data integrity policy” was discussed.
Complaints
The SOP “Handling of customer complaints” and register for 2016 were discussed. No complaints were registered in 2017. Complaints were classified as:

- Critical
- Major
- Minor

- Quality related
- Non-quality related

Recalls
The SOP “Procedure for recall” was discussed. There were no product recalls in the Company history. The following types of recalls were specified in the SOP:

- Class A
- Class B
- Class C
- Statutory recall
- Voluntary recall

According to the SOP mock recall should be performed once in two years.

Supplier qualification
The SOP “Procedure to evaluate and qualify the vendors” and approved suppliers list were discussed. The SOP was applicable for raw and packaging materials vendors.

Critical raw materials and primary packaging materials vendor’s requalification audits were performed every 3 years. Non-critical materials vendors were qualified against a questionnaire.

Vendor audit schedule was presented to inspectors; spot checks showed that the schedule was followed.

Two manufacturers audit reports were discussed.

Contracts
The company had contracted out micronization process and particle size distribution analysis.

Validation Master Plan (VMP)
The SOP “Validation master plan procedure” was discussed. The VMP was applicable for:

- Production systems
- Engineering and utilities systems
- Analytical laboratory / QC systems
Personnel
The current organization chart of the company was available. In general the company had a sufficient number of personnel with responsibilities according to their respective units and departments.

According to the company presentation, the number of full time employees was 221

Personnel were wearing clothing suitable for the manufacturing activities.

Training
The SOP “Training” and training schedule for 2017 were discussed. This SOP was applicable for all employees training. The following types of training were described:

- Induction new recruiter – freshener (oral evaluation)
- New recruits – experienced (oral evaluation)
- On job training / functional training (oral evaluation and written evaluation yes/no/true/false)
- GMP (written evaluation yes/no/true/false)
- Safety training (written evaluation yes/no/true/false)
- Ongoing training (group discussion)
- Self-inspection auditors training (oral)
- Remedial training (oral evaluation and written evaluation yes/no/true/false)
- Training for operator persons
- Post training evaluation

Training records were kept in HR and or concerned departments.

The SOP “Analyst qualification” was discussed. Coded sample was given to analyst under qualification. Analyst had to perform triplicate analysis, RSD between triplicates were specified: for assay tests NMT 1 %, for RS tests NMT 5 %.

Analysts were requalified every 3 years.

A number of employees and analysts training files were discussed.

Job responsibilities for the QC manager and assistant manager, QC executive officer and chemist were checked.

The SOP “Employees medical checks-up and personal hygiene” was discussed. According to the SOP all personnel working in the company shall undergo medical examination annually.
2. **Documentation system**
Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures.

The following, but not limited, documents were discussed:

- “Procedure for initiation, approval, distribution control, storage, review, retention of documents & records”. Documents related to batch production/control were retained 1 year after expiry date of the batch. Documents related to the transfer of technology, process development, scale ups, DMFs, stability data, distribution records etc. were retained for the product life time.
- “Product release for sale”
- “Handling of batch production record”
- “Reprocess procedure”
- “Rework procedure” It was explained that according to the company policy reworking of batches was not performed
- “Procedure for batch numbering, BPR numbering & assigning product code”
- “Procedure for label rolls handling”
- “Handling of returned products”
- “Procedure for preparation of certificate of analysis”
- “Procedure for operation and cleaning of reactors Glasslined (GL)/stainless steel (SS)”
- “Procedure for in process sampling”
- “Procedure for the cleaning of clean room filters”
- “Procedure for the qualification and the requalification of clean rooms”

If there were no changes, documents review period was three years. Documents were stored in QA archive in mobile compactors.

3. **Production system**
In general, production operations followed defined procedures. Process flows and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use. The processing status of major units of equipment was indicated.

Manufacturing operations of product under the scope of inspection were carried out in dedicated blocks.

At the time of the inspection, process validation was not completed.
4. Facilities and equipment system

The following areas were inspected:

- Warehouse for raw materials, intermediates, packaging materials and final products
- Solvent tank farm
- Solvent warehouse
- DM Water Plant
- Manufacturing block E
- Manufacturing block C
- Manufacturing Block A including pharma area
- QA documentation room including label printing
- Laboratory facilities

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. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination. Generally the permanently installed pipework was appropriately identified.

QCL premises were separated from manufacturing facilities. Stability chambers were located in QCD.

Microbiological laboratory was recently constructed and at the time of the inspection equipment/utilities were under qualification.

Utilities

Demineralized water (DM)

The SOP “Procedure for microbial analysis of water” and DM trends for 2016 were discussed. SCD media was used for Total viable bacteria counts (TVBC). Alert and action limits were established.

HVAC system

Re-circulated air, generated by 9 air handling units was supplied to clean rooms located in Block A. Terminal HEPA filters H13 were installed in the rooms. G4, F5 and F9 filters were cleaned weekly. Pressure differentials between G4, F5 and F9 filters were checked and recorded daily using a manually system.

HEPA filters integrity tests were contracted out and performed annually.

Environmental monitoring (EM)

The SOP “Procedure for area count by settle plate method” and EM trends for clean rooms, block A were discussed. Alert and action limits were established.
5. Laboratory control system

Laboratory areas were separated from production areas. Laboratory was operating on 3 shifts continuously. Samples were received via pass box and registered in separate registers for raw materials, intermediates, and finished products.

The following sampling SOPs were discussed:
- “Sampling and release of the raw materials and intermediates”
- “Sampling and release of the packaging materials”
- “Sampling and release of the finished goods (API)”

The SOP “Reserve samples maintenance and quality review” was discussed. Reserve samples were stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer; or for three years after distribution of the batch, wherever is the longer.

The SOP “Procedure for out of specification results”, its flow chart and registers for 2016 and 2017 were discussed. There were separate laboratory incidents log books. According to the verbal explanation laboratory incidents were as an example: system suitability failure, mistaken injection volume, wrong injection sequence, leakage of column etc. It was discussed that there should be SOP describing procedure how to deal with laboratory incidents (documents / instruments / analysis related).

A number of OOS investigation reports were discussed.

The SOP “Working standard evaluation” was discussed. Working standards (WS) were qualified against pharmacopoeia standards. WS were dispensed in single use vials. It was noted that WS dispensed was at the time the LAF was under installation. Reference standards were stored in a commercial type fridge, what was not equipped with an alarm system. Temperature (T) was manually recorded once per day. Usage of reference standards was traceable.

There were two stability chambers available in laboratory for:
- Accelerated stability studies
- Long term stability studies (30 °C and 65%)

T and RH in the chambers was recorded every hour by commercial software and checked once in 24 hours. It was noted that the third stability chamber was under installation. Stability chambers were equipped with audible alarm.

The SOPs “Audit trail review of analytical data for chromatographic / non chromatographic systems”, “Chromatographic practice” and “Backup and restoration of electronic data for stand-alone systems and creation of data path” were discussed.

Specimen signature log was presented to the inspectors.

During the laboratory inspection a number of instruments, log books and calibration records were checked.
Analytical balances were verified daily using 5 standard weights and calibrated monthly for:
- Repeatability
- Weighing profile
- Accuracy
- Sensitivity
- Eccentricity
- Linearity

HPLC grade water was purchased from outside the laboratory.

6. Packaging/labelling system
Packaging / labelling operations were not inspected.

The SOP “Procedure for label rolls handling” and SOP/QAD/026/01 “Procedure for the handling of damaged labels” were discussed.

Roll labels were stored in mobile compactors.

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 corrective actions taken, the API under prequalification process manufactured at Delta Finochem Pvt. Ltd (Block A, Block A Clean Room and Block C) located at Gate no. 350, Village Wadivarhe, Tal-Igatpuri dist-Nashik, 422 403 India was considered to be manufactured in compliance with applicable sections of 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 used for assessing compliance

   Short name: WHO TRS No. 957, Annex 2

   Short name: WHO TRS No. 986, Annex 2

   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

   Short name: WHO TRS No. 961, Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
   Short name: WHO TRS No. 957, Annex 1

   Short name: WHO TRS No. 957, Annex 3

    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    Short name: WHO TRS No. 961, Annex 9
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    Short name: WHO TRS No. 981, Annex 2
    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
   Short name: WHO TRS No. 981, Annex 3
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

   Short name: WHO TRS No. 961, Annex 14
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 992, Annex 3

   Short name: WHO TRS No. 992, Annex 4

   Short name: WHO TRS No. 992, Annex 5

   Short name: WHO TRS No. 992, Annex 6
   Short name: WHO TRS No. 996, Annex 3
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

   Short name: WHO TRS No. 996, Annex 5
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

   Short name: WHO TRS No. 996, Annex 10