

**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
API Manufacturer**

**Part 1: General information**

|                                                                |                                                                                               |
|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Name of Manufacturer                                           | Dong-A ST Co., Ltd.                                                                           |
| Unit number                                                    | Ban-Wol Plant                                                                                 |
| Production Block                                               | Synthesis Building 2                                                                          |
| Physical address                                               | 171, Haean-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Republic of Korea                            |
| Contact person and email address.                              | Mr.Paul Ryu<br>International Business Division<br>Dong-A ST Co. Ltd<br>Email: rsy@donga.co.kr |
| Date of inspection                                             | 27-28 May 2013                                                                                |
| Type of inspection                                             | Routine                                                                                       |
| Active Pharmaceutical Ingredient(s) included in the inspection | Cycloserine (APIMF 118)                                                                       |
| Summary of the activities performed by the manufacturer        | Production and quality control of APIs.                                                       |

## **Part 2: Summary**

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

The site was established in 1983 and is located about 40 km from Seoul. The total site area is about 19,410 m<sup>2</sup> with buildings occupying about 10,312m<sup>2</sup>. There are 59 employees at the site.

Note: The address has changed due to the government changing the system for identifying street addresses. The previous address was 434-3, Moknae-Dong, Danwon-gu, Ansan-si, Gyeonggi-do. There is no change to the physical location.

Block 2 had been almost entirely refurbished since the start of its operations. At the time of inspection the only production in process was a batch of cycloserine undergoing final drying before packaging and QC.

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

The Dong-A Pharm Ban-Wol production site was last inspected by the WHO team in December 2011.

It had been inspected by the KFDA and audited by several large pharmaceutical companies. USP PQM performed a pre-inspection in October 2011.

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

The inspection focused on the production and control of the cycloserine API (including for TB236 and cycloserine supplied to other FPP manufacturers for the manufacture of prequalified FPPs), including corrective actions following the last WHO 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.

### ***Inspected Areas***

Production (technical areas and final powder processing areas of Block 2).  
Documentation, including SOPs and Batch Manufacturing Records (BMRs)  
Quality control laboratory  
Warehouses  
Solvent recovery

## **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. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified.

## **Internal audits**

The SOP for self-audits was reviewed. Self-audits were performed every 3 months. Composition of the audit team was defined with the head of QA being the lead auditor. Self-audits were performed as per a pre-scheduled plan and elements were verified in accordance with a checklist which was prescribed by the local KFDA requirements.

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

The 2012 Annual Product Review for cycloserine was reviewed. It had been done according to protocol and reported. Batches of cycloserine API had been produced during 2012 were included in the review.

The review included reviews of the key starting materials, in-process control and critical API test results, OOSs, deviation, changes to processes and analytical methods, stability, returns, complaints and recalls. Data was analysed for trends using commercially available software.

The PQR concluded that there were no issues with the manufacture of cycloserine and this was supported by the sample of data reviewed by the inspectors.

## **Out of specifications (OOS)**

The SOP for handling OOS test results was reviewed. It was applicable to OOS test results for APIs, raw materials, purified water, environmental controls, intermediates, stability samples, water samples and microbiology samples and covered all test parameters, including visual inspection tests. The SOP specified the rejection of the material if an OOS was confirmed.

No OOSs relevant to cycloserine had been recorded in the log-book viewed.

## **Change control**

Three changes had been recorded in the 2012 PQR for cycloserine. The changes were related to the calculations of condensation substance, calculation of yield and code change of key starting materials. Non-compliances observed during the inspection that was listed in the full report regarding change control management of the second supplier of intermediate were addressed by the manufacturer to a satisfactory level.

## **Deviations**

Three deviations had been recorded in the 2012 PQR for cycloserine. One had also resulted in a change control and was reviewed.

## **Reprocessing**

SOP for reprocessing was reviewed. The company indicated that reprocessing had never been necessary for cycloserine.

## **Rejects**

According to the applicable SOP, rejected starting materials were immediately returned to the supplier. A secure cage for storing rejected materials was available in the warehouse and was empty.

## **Market returns**

No market returns had been recorded for cycloserine.

## **3. PERSONNEL**

### **Personnel Hygiene**

Stringent measures were in place to avoid contamination. Direct contact with intermediates or APIs was avoided. Overshoes, gowning and hand-washing were required in areas where product was exposed. Smoking, eating, drinking, chewing and the storage of food were not allowed in production and storage areas.

## **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. Although space was limited, there was adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. QC areas and operations were separated from production areas.

### **Utilities**

Areas for the final processing and packaging of cycloserine were provided with filtered air to achieve a Grade D standard.

### **Water**

The purified water system was not inspected on this occasion due to the time limitation. The data for water in the PQR showed no abnormal results.

### **Lighting**

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

### **Sanitisation and maintenance**

All areas visited were clean and well maintained. The sample of procedures reviewed was satisfactory.

## **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. Most of the equipment was made of stainless steel.

### **Equipment maintenance and cleaning**

The manufacturing equipment within the block was in an excellent state of maintenance and cleanliness. Cleaning of equipment was carried out according to written procedures.

Food grade oil was used inside the reactors and mechanical grade for the gears located outside.

### **Calibration**

The calibration status of control, weighing, measuring, monitoring and test equipment was indicated on the equipment by calibration label. All checked showed that calibrations had been done when due.

### **Computerized systems**

The company was in the process of installing a LIMS system at the time of the inspection. It was the same system as is operational at the Cheonan FPP site and validation had been contracted out the same specialist company. Validation had not been completed and was not reviewed during the inspection.

## **6. DOCUMENTATION AND RECORDS**

### **Documentation system and specifications**

Activities were generally well documented in SOPs. These were approved and version controlled. Because of the change from Dong-A Pharma to Dong-A ST version history had not been transferred and recorded in the all current SOPs, but all superseded documentation was understood to have been retained for reference. All records and other documentation requested during the inspection were readily available.

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

Records of major equipment use and cleaning showed the date, time, product and batch number of each batch processed in the equipment.

### **Records of raw materials, intermediates, API labeling and packaging materials**

Records of raw materials, intermediates, API labeling and packaging materials were maintained.

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

Master production instructions were available, dated and signed and independently checked, dated and signed by a person in the quality assurance unit.

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

Batch production records were available. These records included a review checklist which was signed and dated by QA. They were numbered with a unique batch number, dated and signed when issued. The synthesis department filled in the required information and it was signed off by the registered pharmacist.

### **Laboratory control records**

Since the last inspection, significant changes to the way that laboratory records were maintained had been made. Detailed records for each test were maintained, chromatograms were printed and it was verified that electronic raw data was also retained. There was a documented procedure for back up electronic records. As previously mentioned, the company is in the process of implementing a LIMS system.

### **Batch production record review**

A batch of cycloserine was in processing of drying step at the time of the inspection. The BMR was available for review.

## **7. MATERIALS MANAGEMENT**

### **General controls**

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available.

Vendor approval procedure was reviewed, and sample testing before approval was not required by the procedure. Approved vendor lists for general raw materials, key raw materials and packaging materials were available.

### **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.

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

### **Production operations**

The manufacturing facility and equipment for cycloserine located in the production block was dedicated to this API. Raw materials were weighed and measured under appropriate conditions in the production area.

The batch size for cycloserine was fixed with the final yield. At the time of the inspection of the production area, a batch of cycloserine was at the final drying stage. The record for this batch had been correctly completed up to this point.

Although this production unit was generally of a good standard, it was noted that the change rooms for entry were rather small. However, given the low number of required operators, this is unlikely to be a problem.

### **Time limits**

Time limits were specified in the BMR where necessary. No deviations relevant to time limits had been documented.

### **In-process sampling and controls**

In-process controls and their acceptance criteria were defined.

### **Contamination control**

The level of protection from contamination of the API during processing was acceptable.

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

### **Packaging materials**

Packaging materials were received, quarantined and released according documented procedures and specifications. Packaging materials were appropriately stored in a dedicated room.

### **Packaging and labeling operations**

After drying, the API was loaded directly into the 2 final containers in the drying room before the weight of each container was adjusted in the packaging room, 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, storage conditions, manufacturing date and re-test date. Non-compliances observed during the inspection that was listed in the full report regarding

that cycloserine API with different code numbers was manufactured and the label did not include information to identify this were addressed by the manufacturer to a satisfactory level.

## **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. Non-compliances observed during the inspection that was listed in the full report regarding tractability of quarantine status on the labels were addressed by the manufacturer to a satisfactory level.

### **Distribution procedures**

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

## **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. Specifications and test procedures were available for cycloserine API, the purchased key intermediate, other starting and packaging materials and recovered ethanol.

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

Testing was performed according to approved specifications, test methods and related SOPs. The records reviewed showed that detailed worksheets were used to record the tests performed including reagent preparation, test parameters, results, calculations, printout of chromatograms and print out of test audit trail where relevant. Retention of electronic raw data was also verified. This was a significant improvement since the last WHO inspection.

### **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 25°C/60% RH.

### **Expiry and retest dating**

The shelf life of the inspected API Cycloserine was 24 months as approved by WHO PQ programme.

### **Reserve/retention samples**

Retention samples were kept for a period of 1 year after the expiry date. Retention samples of starting materials and 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 was reviewed and considered to be acceptable.

## **12. VALIDATION**

### **Validation policy**

The validation policy had not changed since last inspection. It was not reviewed on this occasion due to time limitation.

### **Process validation programme**

Written process validation programme was established. Non-compliances observed during the inspection that was listed in the full report regarding process validation after introducing the new key starting intermediate were addressed by the manufacturer to a satisfactory level.

### **Periodic review of validated systems**

The annual PQR for cycloserine confirmed the satisfactory validation status of validated systems.

### **Cleaning validation**

The equipment used for manufacturing Cycloserine was dedicated. Cleaning validation was not reviewed on this occasion.

## **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. Category 3 required consideration of regulatory status. The SOP stated that customers should be notified of changes when affecting the quality of the product and that the regulatory affairs team should be notified of major changes prior to their implementation. The records for 3 changes were reviewed.

The change to include a second supplier of the key starting intermediate was reviewed in detail and discussed. In 2012 a second supplier of the intermediate had been approved. The internal material control number that had been used for the original supplier was allocated to the CMS from the new supplier. Non-compliances observed during the inspection that was listed in the full report regarding the change control related needs for process validation, and notification to affected customers were addressed by the manufacturer to a satisfactory level.

## **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 BMR), rework or destroy the material was made on a case by case basis. The company stated that it had never been necessary to reprocess cycloserine and this was supported by the PQR.

### **Reworking**

Rework was possible in defined circumstances and covered by a documented procedure. The company stated that it had never been necessary to rework cycloserine and this was supported by the PQR.

### **Recovery of materials and solvents**

Ethanol recovery was carried out by transferring it directly to a distillation plant dedicated to ethanol used in cycloserine manufacture.

Specifications for fresh and recovered ethanol were established to be the same and recovered ethanol was required to be tested and released before re-use. According to the BMR, fresh ethanol had to be used for the final processing stage.

## **15. COMPLAINTS AND RECALLS**

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

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

No manufacture or testing of cycloserine 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, Cycloserine (APIMF 118) manufactured at Synthesis Building 2, Ban-Wol Plant, Dong-A ST Co., Ltd., 171, Haean-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Republic of Korea 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.