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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Dong-A ST Co., Ltd.
Unit number	n/a
Production Block	n/a
Physical address	2F Section B, 3F, 4F Section B, 200-23 Baekseokgongdan 1-ro, Seobuk-gu, Cheonan City, Chungcheongnam-do, Republic of Korea
Contact address.	Paul Ryu (Regional Manager N. America & WHO Business) International Business Division Dong-A ST Co. Ltd Email: rsy@donga.co.kr
Date of inspection	22 – 24 May 2013
Type of inspection	Routine
Dosage forms(s) included in the inspection	Solid oral dosage form (Capsules)
WHO product numbers covered by the inspection	TB236 (Cycloserine 250 mg capsules)
Summary of the activities performed by the manufacturer	Production and Quality control of the OSD and other FPPs.

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Contact: prequalinspection@who.int

Part 2: Summary

General information about the company and site

At the time of the last inspection in November 2011, Dong-A Pharmaceuticals was a listed company. On 1 March 2013 the company re-structured with a new listed holding company and Dong-A ST Co Ltd being created with responsibility for prescription medicines and Dong-A Pharmaceuticals Co Ltd continuing with responsibility for OTC products only.

Dong-A ST operates 3 manufacturing plants:
Cheonan Plant (founded in 2000) – pharmaceutical finished products; tablets, capsules and injectables
Ban-Wol Plant (founded in 1982) – synthetic APIs
Dal-Seong Plant (founded in 1999) – biomedicines

The Cheonan plant is situated in the BaekSeok Industrial Complex in Cheonan. Approximately 228 staff worked at the facility for Dong-A ST at the time of inspection.

Note: The address has changed due to the government changing the system for identifying street addresses. The previous address was No. 404 Chaam-dong, Cheonan City, Chungcheongam-do. There is no change to the physical location.

OTC products are manufactured by Dong-A Pharmaceuticals in a separate part of the plant.

The cycloserine product is currently manufactured for the local regulatory market as well as for overseas markets.

History of WHO and/or regulatory agency inspections

This was a routine WHO inspection following the first WHO inspection conducted in November 2011. The Cheonan plant is inspected and licenced by the KFDA and has also been inspected by the Regulatory Authorities of Brazil, Yemen, Colombia, Jordan, Ukraine and by the USP PQM (pre-inspection).

Focus of the inspection

The inspection focused on the production and control of cycloserine capsules 250 mg (TB236) and included reviewing CAPAs from the last WHO inspection. The product was prequalified on 16 November 2012.

The inspection covered all the sections of the WHO GMP guide, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

On day 1, inspectors reviewed organizational structure, job descriptions, change controls, deviations, product quality reviews, complaints and recalls, contract agreements, supplier approval, as well as the starting and packaging material warehouse and the sampling area.

On day 2, after giving a summary of the observations from day 1, inspectors focussed on items remaining from the previous day such as sampling plans and QRM. Process validation was reviewed and an inspection of the production areas included weighing, blending, encapsulation, packaging, cleaning and in-process controls, conducted.

On day 3, after giving a summary of the observations from day 2, inspectors inspected the quality control laboratory including incoming samples, training, HPLC, reagents, reference standards, packaging materials, OOS, stability chambers as well as retention samples. There was a review of executed batch records, equipment qualification, computer validation, as well as environmental monitoring. Remaining items such as self-inspections were reviewed. The inspection was closed with a list of observations and an unofficial statement on the level of compliance of the site.

2.1 QUALITY ASSURANCE

The company had a well established quality system that was implemented and maintained.

Following restructure in March 2013 the organization chart had been revised. This and a sample of job descriptions were reviewed. The organization chart was not fully accurate and nor was it an approved document. (see observations below)

The 2012 PQR for cycloserine 250mg capsules was reviewed, was generally comprehensive and showed no issues of concern.

Change control procedure, change control log and two changes in 2012 were reviewed.

Vendors were approved according to SOP. Inspection of API suppliers was included and there was an approved list of acceptable vendors. A procedure for delisting suppliers if necessary was included.

A new procedure was available to describe requirements for quality risk management. A QRM committee had been established and QA was involved. The procedure described various QRM methodologies. As an example, the application of QRM to a project to construct a separate facility for manufacturing cytotoxic OSDs was reviewed. The project plan included a detailed FMEA study to ensure that any risks were acceptable.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

All of the necessary aspects of GMPs were covered. The necessary resources were provided, including qualified and trained personnel, suitable equipment, services and premises. Appropriate controls were performed for finished products, raw materials, containers and labels as well as in-process. Manufacturing processes were clearly defined and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that complied with their specifications. Qualification and validation were performed.

2.3 SANITATION AND HYGIENE

A high level of sanitation and hygiene was observed at the plant. All surfaces in production were cleaned on a regular basis. There were no traces of dust or residue.

2.4 QUALIFICATION AND VALIDATION

Since the last WHO inspection the company had installed a new fully instrumented encapsulation machine and a LIMS plus Raw Material Weighing System. Qualification of the encapsulation machine and validation of the LIMS/RWS were reviewed.

The LIMS/RWS system had been categorized according to GAMP as Category 5. Validation had been contracted out to APVS, a specialist company in this area. References included EU GMP, US FDA and GAMP. Because of the large volume of documentation and time available, a sample of the protocols, IQ, OQ and PQ test scripts, test records and the handling of deviations were reviewed. The validation appeared to have been done to a satisfactory standard and no observations were recorded.

Qualification and process validation for new encapsulation machine were reviewed and considered to be acceptable in general. The process validation protocol and report were reviewed.

2.5 COMPLAINTS

Complaints were handled according to SOP. Review of the complaints register showed that no complaints regarding cycloserine 250mg capsules had been received since the last inspection.

2.6 PRODUCT RECALLS

A SOP described the procedure for handling recalls. Since the last inspection a new section had been added to describe the procedure for recalling product supplied outside Korea. Reporting to regulatory authorities, distributors and importers was included, with timelines specified.

2.7 CONTRACT PRODUCTION AND ANALYSIS

No contract agreements were reviewed because this was not applicable to cycloserine capsules.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were performed according to SOP. They were conducted every 3 months so that each area was inspected at least once a year. Checklists provided by the KFDA were used and observations rated as critical, major or minor. Observations were corrected through the CAPA system. The plan for 2013 was reviewed and records showed that they had been done as per the plan.

2.9 PERSONNEL

Job descriptions were approved. A sample for key personnel was reviewed and included the Legal Pharmacist. Responsibility for release could be delegated to a deputy Legal Pharmacist who worked in the validation area. Primary responsibilities were further defined using a matrix of personnel and activities.

2.10 TRAINING

Training of staff in the QC laboratory was reviewed. QC Team training and analyst training was done according to SOP. Training for a newly employed analyst was reviewed. Needs had been assessed and there was a detailed record of what had been done. Non-compliances observed during the inspection that was listed in the full report regarding training were addressed by the manufacturer to a satisfactory level.

2.11 PERSONAL HYGIENE

All of the necessary requirements were fulfilled. Full gowning was in use in all of the production areas.

The gowning procedure in the sampling room was reviewed.

2.12 PREMISES

Manufacturing areas and the QC laboratory were generally of a good standard. Pressure differentials between each zone and manufacturing rooms were monitored and recorded. Since last inspection the production area had been improved by installing floor to ceiling glass walls in the central area.

A major expansion of the material warehouse was under construction at the time of the inspection. Temporary arrangements for material access had been made, but a temporary cover to the entrance had to be removed to allow access to the construction area.

2.13 EQUIPMENT

Equipment was generally of a good standard, clean and well maintained. Since the last WHO inspection some new equipment had been installed, e.g. new encapsulation machine and new equipment for checking the text of printed packaging material.

Equipment was not dedicated in general. However, an IBC for mixing, storage and transfer to the encapsulation machine was dedicated by means of labelling and reference in the BMR. The cleaning procedure for the IBC was reviewed.

2.14 MATERIALS

Materials in the warehouse were appropriately stored in a clean and orderly manner.

Laboratory reagents were labelled with an expiry date based on either the manufacturer's expiry date or an expiry date based on whether the material was solid or liquid from the date of opening.

2.15 DOCUMENTATION

Activities were generally well documented in SOPs. These were approved and version controlled. All records and other documentation requested during the inspection were readily available. Since the last inspection, all SOPs had been amended to reflect the change in company name. 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.

Batch numbers were determined by year, month and serial number. Non-compliances observed during the inspection that was listed in the full report regarding batch numbering were addressed by the manufacturer to a satisfactory level.

The Master Batch Record for TB236 cycloserine 250mg capsules was reviewed. As no PQ product had yet been made an example of cycloserine 250mg capsules for another market was reviewed. The weighing record sheets for starting materials were not available in the master BMR but were printed during production.

2.16 GOOD PRACTICES IN PRODUCTION

Cycloserine capsules were not being manufactured at the time of the inspection and there were no other activities in most of the areas used for this product.

Material dispensing was performed in an area equipped with a well designed booth. Two balances were available for weighing and were periodically checked and were calibrated annually. Powders were mixed in a dedicated tote bin that could then be inverted on the encapsulation machine. A common room for in-process controls was available and suitable equipment was available. The packaging area included suitable protection for exposed product and good segregation between packaging lines.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Starting materials were sampled according to SOP. For materials received in quantities of 30 or less containers, every container was checked for ID using NIR. For more than 30 containers and all sampling for other tests, sampling was based on the n-plan. Considering that the API and only single excipient for cycloserine capsules was received in quantities considerably less than 30 (typically 2 containers), this was accepted for this product.

Sampling of packaging materials was based on AQLs. Approved specifications and reference specimens were available. Because some packaging materials were in languages that could not be understood, new equipment to verify printed material text against an approved sample had been purchased. The desiccant foil used for cycloserine capsule blister packaging was checked for pin-holes using a light-box.

OOS test results were handled according to SOP. The procedure was acceptable and the OOS register showed that none relating to cycloserine 250mg capsules had been recorded.

The specifications, HPLC test method for assay, worksheets, test records and equipment maintenance were available for inspection. Tests followed the instructions given in the relevant written test procedure. For each batch of medicines product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

The QC laboratory visit also included an inspection of stability chambers and retention sample store. A written programme for stability test control was reviewed. Temperature in the incubator was continuously monitored. Incubators were equipped with alarm system.

Retention samples from batches of finished product as well as related documents were kept for one year after the expiry date. Finished products were kept in their final packaging.

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, Dong-A ST Co. Ltd. Cheonan Plant located at 2F Section B, 3F, 4F Section B, 200-23 Baekseokgongdan 1-ro, Seobuk-gu, Cheonan City, Chungcheongnam-do, Republic of Korea 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.