

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1	General information
Manufacturers details	
Name of manufacturer	Dong-A ST Co., Ltd. (Cheon-An Plant)
Corporate address of manufacturer	64, Cheonho-daero, Dongdaemun-gu, Seoul, Republic of Korea
Inspected site	
Address of inspected manufacturing site if different from that given above	2F Section B, 3F, 4F Section B, 200-23, Baekseokgongdan 1-ro, Seobuk-gu, Cheonan City, Chungcheongnam-do, Republic of Korea
Unit / block / workshop number	3rd Floor Workshop + related areas
Manufacturing license number,	Manufacturing license number 1290, MFDS-6-F-1290-1-2016-33 (GMP compliance certificate from KFDA, Daejeon Regional Commissioner Food and drug Administration) , issued on 2016.07.13 (expiring 2019.07.12).
Inspection details	
Dates of inspection	14-17 November 2016
Type of inspection	Routine
Introduction	
Brief summary of the manufacturing activities	Oral solid dosage forms (OSD): tablets, capsules, powders were manufactured There were 97 products listed on the listing for OSD products (11 capsules, 1 dry syrup bulk, other products were tablets – coated and uncoated) Injectables: vials (freeze-dried, liquid), ampoules (freeze-dried, liquid), cytotoxic and non-cytotoxic products are produced at the injection manufacturing area.
General information about the company and site	1st floor: PW system and packaging material warehouse. 2nd floor: raw material warehouse and packaging material warehouse. 3rd floor: OSD manufacturing area, finished product warehouse and AHU. 4th floor: injections manufacturing area, QA office and QC laboratory, AHU.
History	It received the following inspections during the last three years: -March 2013: Ukraine MOH -May 2013: WHO -August 2013 and September 2013: MFDS (Cytotoxic and Injections) -April 2014: PMDA, Japan -September 2014: ANVISA, Brazil

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

	-April 2015: MFDS, Korea -June 2016: MFDS, Korea -June 2016: INVIMA, Colombia
Brief report of inspection activities undertaken, scope and limitations	
Areas inspected	Production floor, Utilities, Quality Control.
Restrictions	Not applicable
Out of scope	Not applicable
WHO products covered by the inspection	Anti-Tuberculosis

Abbreviations	AHU	air handling unit
	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
	FBD	fluid bed dryer
	FMEA	failure modes and effects analysis
	FPP	finished pharmaceutical product
	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
	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

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

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
---------------	---

1. Pharmaceutical quality system

Procedures were available: The SOP for Quality Risk process was implemented in 2013 and used for the general description of the system and methods. The QRM project “Retrospective risk assessment for quality system (oral solid dosage forms)” was reviewed. During this detailed assessment, all risk factors of production of solid dosage forms at the site were evaluated. As result, it was identified that each risk factor was reduced to an acceptable level according to GMP policy and management procedures. Evaluation of the risk occurring from compressed air was missing during the evaluation. The general risk of contamination of the products in the production area for solid dosage forms by API’s from the area for production of cytotoxics, was reviewed. Evaluation was done together with the implementation of separate production area (project master plan. Project plan was done together with change control. Containment methods for highly bioactive substances were implemented. A dedicated air handling system without recirculation was installed. Exhaust air was filtered through serial double HEPA filters. The completion report of change control was available. Finalization of the change with regards to qualification was approved.

Product Quality Review

Product Quality Review was performed adequately. Cpk values were calculated and limits were established. Equipment qualification tests performed in 2015 were listed. AHU qualification tests were described to have been done in 2015. The temperature and the humidity were described adequately. OOS procedure SOP entitled “Out of Specification, QC Laboratory”, was reviewed. It was very detailed and specified each possible step using flowcharts. The SOP on deviations was reviewed. Deviations were classified into four categories: critical, major, minor and “error”. Investigations on deviations were done by the responsible person of each department and by the QA team

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

Deviations:

The SOP on deviations was reviewed. Deviations were classified into four categories: critical, major, minor and “error”. Investigations on deviations were done by the responsible person of each department and by the QA team. The registers for 2015 and 2016 were maintained electronically. The 33 deviations for 2016 and 39 for 2015 were reviewed. Deviations classified as “errors” were kept on a separate electronic list. There were 80 errors reported on the list for 2016. Recurring deviations were dealt with by implementing appropriate CAPAs, such as retraining.

Change controls.

The SOP for change control was reviewed. The SOP stated that when a change that would require regulatory filings gets approved, the responsible department’s regulatory affairs team is informed and they will prepare the documents for the variation. Changes were classified into 3 levels: level 1, being a change that does not affect the quality of the product and not requiring a qualification (e.g., label on entrance to the working area); level 2, being a change that could impact product quality, such as a change to the test method or to the testing equipment; level 3 is a change that will affect product quality, such as a change in manufacturing method or that would require involvement of regulatory affairs (for instance, a change in the manufacturing process or ventilation system). There were 60 change controls filed in 2016. One of the changes for the use of an additional blister packaging line, was reviewed. A detailed form was used which included the assessment of the needs for each of the different possible types of qualification/calibration and validation (process validation, cleaning validation, computer validation, method validation, media fill).

In the example of an addition of a new product to an existing line in production, there was no risk assessment of the potential cross contamination of the product with other products being manufactured at the site, such as cytotoxics and/or anti-cancer compounds. A general risk assessment was nevertheless available and was reviewed.

2. Good manufacturing practices for pharmaceutical products

All 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.

3. Sanitation and hygiene

The SOP entitled “Personal Hygiene” was reviewed. It provided instructions for cases of health issues in personnel. Each member of personnel was required to get a medical check before starting work at the company. It stated that hand-washing was required prior to entering production. Employees with scars or diseases were prohibited from working. Workers conditions which can affect the product should be reported to division heads and managers.

4. Qualification and validation

Validation Master Plan

The validation master plan for the Cheon-An plant, was reviewed. Most validation was to be done prospectively. Concurrent validation could be done only in exceptional cases where justified. Retrospective validation was not being done in practice. A matrix identified all validation/qualification/revalidation to be done during the year. Method validation was described in the master plan. The need to perform analytical method revalidation was done every five years according to an SOP.

Computer system validation: the manufacturing process and the computer systems which are already existing and used for manufacturing and quality management, as well as newly brought in computer systems were covered by this document.

Cleaning validation

The general description for cleaning validation was given in an SOP. Methods used for calculation of the limits for maximum allowable carry-over of product residues (MAC) were the 10 ppm criteria and the 0.1% of the normal therapeutic dose criteria. The more stringent of these two options was used. Visually clean criterion was not mentioned. However, in the SOP it was clarified, that the equipment should be visibly clean. Otherwise, additional sampling would be required. Additionally, operators had to document in the cleaning reports, that the equipment was visibly clean after cleaning. The cleaning validation report for the mixing container, used for mixing process with a mixer was reviewed. A mixing container was used as dedicated equipment for the products. However, cleaning validation was done to show the possibility of appropriate cleaning during the process. Revalidation was done because of the extension of production campaign to 16 lots. Risk assessment was documented together with the selection of the sampling points for the swabbing. Calculation of the limits was explained in detail. Limits of detection / quantification were validated and found below the limits calculated for swab sampling (sampling of 25 cm², solvent methanol was used). Recovery factor for swab sampling was calculated (>75%) and taken into consideration. Microbial evaluation for bacteria, fungi and absence of specified microorganisms was done. Further, cleaning validation protocol for capsule filling process, using filling machine, capsule weighing machine, capsule metal detector and visual screening machine were checked. Calculation for the worst case product was done on the basis of the dose, solubility, LD50 and batch size. Pranlukast capsules were chosen as the worst case product. Limit of 6.54 µg /cm² (8.18 µg/mL) was calculated for the capsule weighing machine. Limit of 2.62 µg /cm² (3.28 µg/mL) was found for the capsule filling machine. No API was found during the analysis. LOD / LOQ were given with 0.063 / 0.191 µg/mL. Successful cleaning was confirmed during 3 batches.

Status of qualification:

A qualification matrix was available. According to this matrix, qualification of relevant equipment and utilities was done. Revalidation dates were fixed in the schedule and controlled by QA.

Process validation report

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

According to the information available during the inspection, the manufacturing process was without any change since the last WHO inspection. Qualification and process validation for the new encapsulation machine was reviewed during the last inspection. There was no additional review done during this inspection.

5. Complaints

The complaints were reviewed. It included a flow chart specifically describing each step of the procedure. If it takes more time than expected, a draft reply is given to the customer first, unless the investigation can be completed rapidly. In section 5.5 of SOP, the numbers of days to respond were given, depending on each individual scenario. If there was a substance that should not be in the product, or if the product was spoiled, a reply should be provided within 5 days and a final reply within 15 days. The draft replies were not an obligation – the shortest timeline should apply. In case a microbiology test was necessary, then the complaint would be responded to within 17 days. If there is a serious complaint, the claim committee deliberates on whether the product should be recalled/retrieved from the market.

The complaints register was reviewed. Minor observations were raised which were addressed by the company by means of CAPA.

6. Product recalls

The SOP was reviewed. It contained flowcharts explaining the procedure.

A mock recall was done in June 2016 for an export product, with Brazil as destination according to company's policy to conduct a mock recall once every two years if there was no actual recall. Documentation indicated the system was effective.

7. Contract production, analysis and other activities

Quality agreements were reviewed. In one of the examples reviewed, a table defined and allotted responsibilities between the two companies. All raw materials were Dong-A's responsibility (purchase, testing, release, etc.). Only release of bulk products could be done by Suheung, not by Dong A. This was found to be adequate for its purpose.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections were called "internal audits". Supplier audits were also performed prior to the approval of new suppliers.

Internal audits

The SOP entitled "the manual of self-audit", was reviewed. There were three self-audits scheduled in 2016, one for solid oral and injection dosage forms, another one for solid orals and a third one for imported and consignment products. The report from the self-audits performed were reviewed.

Supplier approval

The job manual document entitled "Audit Program control of QM Team" was reviewed. Through GMP questionnaires (of 31 pages each) were sent to suppliers. For a new supplier, they always perform an on-site audit, whether it's packaging materials and excipients. The qualified supplier list was reviewed.

9. Personnel

In total, there were 125 employees in production, 28 in utility management, and 15 in general affairs and 103 in the quality unit.

The job descriptions of the legal Pharmacist, from QA, who was entitled to release batches along with a personnel from production, were reviewed. Job descriptions included a matrix of responsibilities for the legal pharmacist.

10. Training

The document entitled “Education & Training control” was reviewed. It included a training matrix which listed the training needs in each area of GMPs for each of the different teams at the company and it also distinguished the needs of existing employees from those of new employees. For employees that are already in the same department within the company, only 4 hours of GMP training was given per year internally. External training was also given by other companies. Company introduction, facility introduction, general information about manufacturing and management teams, GMP generals, safety and GMP issues, SOPs and on the job trainings which include test procedures as well as on the job training.

11. Personal hygiene

Please refer to section 3 “Sanitation and Hygiene”.

12. Premises

Handling of cytotoxic products

Storage of API's, sampling, dispensing and production of cytotoxic API's was done at dedicated areas on 4th floor.

Clean zone concept

Primary production area and primary packaging was classified as zone D. Secondary packaging was done at grade E area.

Pressure differentials

Differences in pressure between the different manufacturing rooms, airlocks and zones were appropriately defined (+5 Pa in between different rooms, + 15 in between different zones).

The pressure difference in between primary packaging and secondary packaging was defined with +15 Pa.

Environmental Monitoring

The SOP “Environmental monitoring and acceptance criterion for cleanliness” was reviewed. Alarm and action limits were defined and revised every two years based on trending results. According to the SOP, baseline monitoring was done at operation. For grade D area, monitoring of particles and cfu should be done quarterly. Reports for 2nd and 3rd quarter of 2016 were available. Sampling points were defined in the “Classification protocol for cleanrooms”. Reporting was done per AHU. Results for AHU 13 and 14 were checked. Single results were all found in specification for at rest (particles class D) and operation (cfu class D).

Utilities

Utility core for manufacturing at the 3rd floor was located at the side of the building opposite from the HVAC area. Installation of air dedusters, AHUs for special equipment (Fluid bed drier) and purified water storage tank for production was done at this area.

HVAC-Systems

15 AHUs were installed for the production area on 3rd floor (manufacturing of oral solid dosage forms).

The installations area was visited and found well designed and in a clean state. Appropriate labelling of the AHUs was done (qualification labels, filter logs). Pressure differences at the medium and final (HEPA) filters were monitored. Limits were defined to see problems during the time of usage.

Documents for qualification of HVAC units relevant for processing of products were requested.

Example, AHU 14: This AHU was installed to supply the dispensing and the washing room.

Number of air changes was specified with > 20 changes per hour. Results of the checks were in between 21 and 121 (for weighing room). OQ tests were done in April 2012. PQ was finalized in April 2014. Additional test report for recovery time for AHU-14 was available, done in July 2016. Measurement was done for 3 rooms. These rooms were chosen based on the usage of the rooms (risk evaluation). Issue pertaining to guidelines used was observed. And contaminations conditions were not defined before start of test. During the recovery test, measurement of particles was done 30, 60 and 90 minutes after starting the relevant AHU. Limits were fulfilled during every measurement. Recovery time was given with 45 min.

Test reports for double HEPA filtration installed for the exhaust air from the manufacturing area for sterile cytotoxics were also available. HEPA Filter integrity tests were done for all AHUs on an annual basis.

In general the AHU system was maintained at acceptable GMP levels. Issues raised were appropriately and promptly corrected by CAPA raised.

13. Equipment

Compressed air qualification / monitoring

The compressed air generation plant was situated at the 1st floor (general utility area). Five (5) compressors (oil class 0), refrigerated / desiccant air dryers and appropriate gas filters were installed. Dewpoint was shown with < 90°C. The SOP for “The quality control method of oil free compressed air & N2 Gas” was available. Oil content was specified with 0.1 mg / m³. Testing was done every 6 months. User points were chosen based on risk assessment (direct contact with the open product). Lists of user points together with the type of usage were available. However, this was not a controlled document in the moment and should be added to the SOP and / or qualification documents for the distribution system. IQ and OQ for compressed air system were done in the 2015. The final report (07/Aug/2015) was reviewed. The distribution system was made of stainless steel.

Preventative maintenance

The schedule for preventative maintenance was reviewed and found to be adequate overall. Minor issues were resolved in the company CAPAs.

14. Materials

The raw / packaging material warehouse was on the 2nd floor. Materials in the warehouse were appropriately stored in a clean and orderly manner. All raw material and packaging materials are received at the warehouse. On receipt of the material, the warehouse person checks the supplier's documents accompanying the materials. The warehouse accepts an only material from approved vendors. A control number is assigned for each batch of material. "Under Test" labels equal to the number of containers are generated by the defined procedure and pasted onto each container. The materials are stored in a separate "Under Test Area". "Separate areas for raw material sampling and NIR testing were seen. Airlocks for materials and personnel were installed.

Based on the results of testing, approval or rejections were documented and the warehouse was informed. Storage areas for approved materials had a suitable size. Separate areas for rejected materials were available. All areas were acclimatized. Building management system was installed. Mapping was done to find the correct installation places for sensors used for monitoring. Manual documentation of monitoring results was additionally

done. Foils for primary packaging were stored at humidity controlled area ($\leq 40\%$ RH). Amounts of incoming material were documented directly to the RWS (Reliance Warehouse System). Retention samples were stored in a separated and locked area at $15 - 25^{\circ}\text{C} / \leq 65\%$ RH. Cleaning logs were available (documentation by cleaning personnel, approval responsible personnel).

Approval of raw materials / release of finished products

Receipt and test on Talc Lot 2803, internal batch 1610469 was reviewed.

Test certificate from March 2016 was available. Full analytical and microbial testing was done.

Documentation for microbial testing was seen in detail. Testing was done. Raw data and incubation parameters (5 days) were documented. QC manager approval was documented. Finished product of batch 1610469 was reviewed. Release by the QA manager was documented.

Purified water

Schematic drawing for water purification system was seen and compared with installation on site. After pretreatment of city water, reverse osmosis, electro deionization, and UV sterilizer was implemented.

All tanks and pipelines are made of stainless steel. Vent filters were present on the storage tanks. Log book was available. UV lamps were checked for intensity and changed every 8000 hours. Monitoring details are given.

15. Documentation

The document control procedure SOP, effective since 201 and the formulation and revision of the Document by another SOP, were reviewed. The purpose of the SOP was to review and approve all documents generated at the manufacturing site. The validity period was defined to one year for SOPs. After one year, a decision is made to extend SOPs for another year, and this could be repeated for up to four years. The person in charge of document control would make the decision on whether to extend an SOP or not. Expiring documents are identified during the monthly check of document expiry dates. Expired documents were stamped with a red expiration label. After an SOP is expired, all of the copies in use are retrieved. Training was done on the new SOPs prior to their becoming effective.

Master Batch / Packaging Records

Master batch records for the several production steps and master packaging record were available.

Documents for every batch are distributed by QA based on the paper version of the MBR / MPR.

Batch record

Batch record for product of batch 1610469 was reviewed: Talc and cycloserine were used as raw materials.

Dispensing was documented with the electronic documentation system in place (part of the automatic raw material weighing system). Blending was done with appropriate equipment. Product was mixed in the drum with equipment identified. This was dedicated for cycloserine products. After mixing (25 min / 5 rpm), transfer and holding was done in plastic bags contained in SS drums. Capsule filling was done and took 2.5 hours. Weight of 20 capsules was checked at the beginning and found in acceptance range. Additional 100% gravimetric weight control by online checkweigher was part of the filling line. Blistering and secondary packaging was done. Shelf life was 30 months.

16. Good practices in production

Production and packaging area was inspected in detail, included weighing, blending, encapsulation, primary and secondary packaging, cleaning and in-process controls conducted. Production equipment was found in good condition. All relevant status and cleaning labels as well as qualification and calibration labels were fixed. De-

dusters were installed in all relevant areas and connected to central dust collection system. Numbering of user points for compressed air was missing from the capsule filling area. Air supply and exhaust air filters were numbered with the number of the related AHU. Pressure differences in between the production rooms were found well controlled with appropriate documentation.

Production process was followed as described in the batch record (see above). However, there was no production of capsules scheduled during the inspection week.

Three (3) dispensing boots with different size were installed at the area for solid dosage forms. Weighing of products was done in dispensing room. The room was found temperature and humidity controlled (19-25 °C, 60% RH). Checking of scales with calibrated weights was done daily. BOHLE mixer was installed at mixing room. Capsule filling was done in a dedicated room. Capsule Filling Machine was installed together with implemented checkweigher, metal detector, and visual screening machine. Qualification and requalification dates were provided. BOHLE container Washer was installed in Equipment cleaning room.

Cleaning agent was used. Certificate was checked before usage. SOP for the managing of detergents was available. Several points of use for water and compressed air was available and labelled. Automated cleaning process was documented. Conductivity check was implemented. IPC laboratory was found well equipped. Automatic Tablet Testing equipment was installed for weight and hardness checks. Three (3) packaging lines for PTP (press-through-packages) and 3 lines for bottle filling were installed. Camera and weight controls were installed at the lines for PTP. Calibration of the weighing units was documented. However, periodic controls of the rejection units were not documented. The observation was well noted and CAPA made to address them.

17. Good practices in quality control

CAPAs last inspection

Some issues were observed on the operations of HPLC. According to the evaluation SOP for “The management method of the using authority for automatic instruments” was revised after the last WHO inspection.

QC laboratory

During the tour the whole process of sample handling was explained.

Handling of samples and analytical data was supported by the LIMS / RWS system (LIMS plus Raw Material Weighing System). System was checked in detail during the last WHO inspection. There was no additional evaluation of details during this inspection.

Modern equipment for testing the product's API and products was available (e.g. UV-VIS Spectrometer Varian, Karl Fischer titration for water (moisture) determination, equipment for dissolution testing, HPLC equipment with Chromeleon 7 CDS, GC testing for residual solvents). Reagents in use were labelled appropriate. List and procedure for handling of standards was available. The list of equipment was reviewed.

System qualification was reviewed for systems operated by Chromeleon. The documentation reviewed had been produced by Thermo Scientific “Installation Guide for upgrading Chromeleon 7 for Chromeleon Domain Controller, Data vault Server and Terminal Servers”. Reference standards were tracked and inventoried using LIMS. The reference standard for product was shown and was from a reliable source. The primary standard was USP Lot H1J318. With regards to reference standards: the secondary standard was procured from an authentic source. It was qualified by Dong A using the USP standard. It had a shelf life of 3 years. Chromeleon 7 was installed on approximately 40 systems. Empower 3 software was installed on a similar number of systems.

Batch release

This inspection report is the property of the WHO

Contact: prequalification@who.int

The SOP entitled “General Procedure for approval of test” was reviewed. Its purpose was to establish guidelines for QA to ensure the quality of incoming raw materials and finished goods release. The responsible pharmacist, from QA, was entitled to release batches along with another personnel from production. Documents reviewed for batch release included all test records, batch records, deviations and OOS, change controls, purified water and environmental monitoring as well the import license.

Batch release documents were signed electronically through LIMS. Microbiological plates were all photographed with dates and included in the batch document package.

Performance verification of balances was performed automatically. They were calibrated only once every six months by the representative of supplier using weights going only as low as 2 g (although the lower range limit was specified to be 20 mg on equipment labels). GWP verification certificates were issued by supplier and one was verified. According to the service agreement with supplier, recommendations were made by supplier to test for minimum weight (by service) quarterly, linearity (by service) quarterly, eccentricity (by user) quarterly, repeatability (by user) monthly, sensitivity (by user) weekly and internal adjustment (by balance) to be done daily. It was explained that this was a semi-micro balance. The micro balances were used instead to weight items lighter than 100 mg. Verifications performed for one of the microbalances were done using a standard weight of 50 mg for the sensitivity test.

Stability test results supporting the thirty-month shelf-life were reviewed for ongoing stability. Batch 1309033 manufactured on 2013-09-06 was reviewed. USP36 was used as the reference.

HPLC analysis for cleaning validation

During evaluation of cleaning validation report for the mixing container, used for mixing process with (BOHLE PM600) was reviewed. No contamination of equipment after cleaning was detected. HPLC method for assay of the API of the product was used.

Control of HPLC analysis showed 2 peaks for the cycloserine in the chromatograms for the measurement of the standard solutions. However, in case of the analysis of finished products and API, only 1 API peak was seen in the relevant chromatograms. From the explanation by DONG-A ST, higher amount of buffer with different pH could influence the chromatographic behavior of the API. Documentation with respect to this was not available. A CAPA was raised to correct these observations.

Monitoring of purified water

SOP on purified water control was available and reviewed.

TOC testing was part of the monitoring. Additionally, online measurement was implemented in the distribution system. Alert limits were set at 30 cfu for Bioburden, 1.1 $\mu\text{S}/\text{cm}$ for conductivity, 5.3/6.5 for pH and 0.3 ppm for TOC. All points of use were sampled at least monthly. PW-EDI-A, PW-EDI-B (both at the supply from the water plant to the distribution system), PW-23, PW-39 and PW-42 (all at the loop returns) were sampled daily.

Loop 3 was at 75–85 °C (hot water for cleaning). The other 2 loops were held on < 25 °. Reports for 2nd and 3rd quarter 2016 were available and checked during the inspection. These were approved by QA, production and head of QA/QC department. And these were found to be satisfactory.

Microbiological laboratory

Nine (9) people were employed at this department. Access to the microbiological laboratory was through airlocks for personnel and material. Airlocks were at overpressure in relation to the corridor. Magnehelic gauges for monitoring of pressure differences in between the rooms of the area were installed. Several testing rooms were set up equipped with safety cabinet. Four (4) incubators, qualification and calibration labels, requalification every year),

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

Growth promotion test

Testing was implemented. Last documentation for the R2A Agar was checked.

Test was done on 03/Nov/2016. Incubation was done for 5 days.

Quantified pellets with *Pseudomonas protegens* and *Methylobacterium extorquens* were used. Recovery was calculated and found near to 100%.

Validation of microbial test procedure for finished product.

The report for suitability of the counting method in the presence of the product was reviewed. Complete validation was available. However, no suitable neutralization method could be found. As a result, the test was performed with the highest dilution factor compatible with microbial growth and the specific acceptance criterion (as described in the USP). The issues observed and raised were corrected by the company through a CAPA.

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, ***Dong-A ST Co., Ltd. (Cheon-An 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 good manufacturing Practices for pharmaceutical products.

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

1. 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.
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. 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/>
3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth 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/

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

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

This inspection report is the property of the WHO

Contact: prequalinspection@who.int

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. Fiftieth 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. Fiftieth 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. Fiftieth 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. Fiftieth 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