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CERTIFICATE OF TRANSLATION

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Title of Document (Description of Service)	Pharmaceutical Manufacturing • Quality Control Report
Name of Customer	Dong-A ST

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IN TESTIMONY whereof, I have here onto subscribed my name and affixed my seal of office.

Date: December 3, 2019

Korea Public Translators Administration Association Translation Office Certified Translators CHOI, GI CHOUL
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Nation of the people, the righteous Republic of Korea

Daejeon Regional Korea Food & Drug Administration

Recipient: Dear representative of Dong-A ST Corp. (Zip Code 31093
200-23 Baekseokgongdan 1-ro, Seobuk-gu, Cheonan-si, Chungcheongnam-do,
Republic of Korea (2F Section B, 3F, 4F Section B)

Title: Provision of GMP Inspection Report Manufacturer (Notification)

1. I wish you tremendous success in everything you do.

2. Regarding your request based on World Health Organization (WHO)'s recent GMP inspection report according to export or your pharmaceutical ('Closerin Cap. 250mg (Cycloserine) (Export Name: Dong-A Cycloserine 250mg)'),

3. We provide you a GMP inspection report prepared in accordance with our 2019 regular pharmacy monitoring on your company as an 'attachment', so please make sure that you do not use it for any other purposes other than the requested one.

Attachment: Pharmaceutical GMP status report (enclosed) 1 copy. End.

Chief of Daejeon Regional Korea Food & Drug Administration

Action Officer		Medical Product Safety	Decision Date 2019.10.24
Assistant	Joh Gyeong Jin	Manager	Song Hyun Soo

Performed by Medical Product Safety Division (2019. 10. 24) Accepted
Zip 35209 155 Chungsa-ro (Dunsan-Dong) Seo-gu, Daejeon Metropolitan City / http://www.mfds.go.kr
Phone number 042-480-8757 Fax 042-480-8770 / ckjkeen@korea.kr / non-disclosure (6)

Jobs are growth and welfare

Pharmaceutical Manufacturing • Quality Control Report

Company Name: Dong-A ST Corp. (1st factory)

Report Offer Number: Daejeon Office-Medical Product Safety Division-**GMP-2019-1**

Report Offer Date: **2019. 10. 23.**

Ministry of Food and Drug Safety
Daejeon Regional Korea Food & Drug Administration

Table of Contents

Report on investigation of manufacturing and quality control standards of pharmaceuticals

1	**Manufacture name and location**		**Name & full address of inspected site**
Manufacture name: Dong-A ST corp. Location: 200-23 Baekseokgongdan 1-ro, Seobuk-gu, Cheonan-si, Chungcheongnam-do, Republic of Korea (2F Section B, 3F, 4F Section B)			
Representative			Dae Sik Um
Head of manufacturing department		Jun Pyeong Lee	Head of quality (warranty) department
2	**Activities carried out by the company [Mark O in the space provided]**		**Activities carried out by the company**
Raw material medicine manufacturing (sterile / non-sterile): N.A/ Completed medicine manufacturing (sterile / non-sterile): O [Solid contents (refined, capsulant, acidic), injectors (injective, freeze-dried injection), cytotoxic anti-cancer drugs (injectors (injective, freeze-dried injection))] Intermediate product manufacturing (sterile / non-sterile): N.A Packing: O Importation: N.A Exportation: O Test: O (biochemistry test, microbiological limit test (non-sterile), sterile test) Others ( )			
3	**Inspection date(s)**		**Inspection date(s)**
2019. 5. 28 (Tue) ~ 5. 31. (Fri) (4 days)			
4	**Inspectors**		**Inspectors(s)**
5	**References [civil service reception number, manufacturing license number, etc]**		**References**
6	**Summary [brief description of the company and processes, previous inspection date, key changes since previous inspection, inspectors involved the previous survey]**		**Introduction**

– Manufacturing plant overview

Area of manufacture (m^2)	Workstation	9,467	Storage	3,192
	Laboratory	1,540	Others	4,301.25

<table>
<tr><td></td><td>Total</td><td colspan="6">185,000.25</td></tr>
<tr><td>Inspected workstation (Completed)</td><td colspan="7"><table>
<tr><td>Form / Classification</td><td>Content solidifying system</td><td>Injections</td><td>Collyrium</td><td>Content liquid</td><td>External solution</td><td>Unction</td><td>Other</td></tr>
<tr><td>Pharmacopoeic type (general agent)</td><td>O</td><td>O</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td>Inspected workstation (Raw)</td><td colspan="7"><table>
<tr><td>Manufacturing method / Classification</td><td>Synthesis</td><td>Fermentation</td><td>Extraction</td><td>Other</td></tr>
<tr><td>General raw material</td><td colspan="4" rowspan="2">N/A</td></tr>
<tr><td>Sterile material</td></tr>
</table></td></tr>
<tr><td>Special agent manufacturing status</td><td colspan="7">□ penicillin agent □ sex hormone agent □ cephalosporin agent
■ cytotoxic anti-cancer agent □ none</td></tr>
<tr><td>Manufacturing status other than medicine</td><td colspan="7">□ food manufacturing □ food additive manufacturing □ healthy food manufacturing
□ medical device manufacturing □ cosmetics manufacturing ■ none</td></tr>
<tr><td rowspan="2">Working personnel (parentheses are pharmacists</td><td>Manufacturing department</td><td colspan="2">110 people (3)</td><td>Head of quality (warranty) department</td><td colspan="2">118 people (4)</td></tr>
<tr><td>Other workers</td><td colspan="2">55 people (0)</td><td>Total</td><td colspan="2">283 people (7)</td></tr>
</table>

- GMP designation history (proof attached separately)
- Designation date: 2016.07.13~2019.07.12
- Form:
  - ■ content solidifying system (refined, capsulated, acidic)
  - ■ injectors (injective, freeze-dried injection)
  - ■ special agent (cytotoxic anti-cancer drugs (injectors, freeze-dried injection))
- Previous inspection record
- Inspection period: June 13~17th, 2016 (5 days)
- Inspection range: investigation of manufacturing and quality control standards of pharmaceuticals (content solidifying system, injectors, special agent)
- Inspection area: manufacturing and quality control area, utility, storage
- Key changes since previous inspection
- Human (manufacturing manager) related:
  - ■ 2016.10.14 manufacturing manager abolition (Sang Chul Kim, Jae Yeong Jang)
  - ■ 2017.11.27 manufacturing (quality) manager change report (Take Geun Kim → Jae Yeong Jang)
  - ■ 2018.05.04 change of representative (Su Hyeong Kang → Dae sik Um
- Machinery and facilities (including facility structure changes) related:
  - ■ 20161227 Agent team 2 Layout change due to installation of Auto Coater and disposal of existing equipment

	■ 20170705 Layout change of Vial dispensary of general injectors ■ 20180130 Layout change of workstation of anti-cancer injectors ■ 20181005-2 Agent team 3 relocation and change of equipment due to bottle packing line 1,3 interlocking establishment <1st>

7	**Summary of inspection performed [inspection range, research area, interviewer during inspection]**	**Brief report of the inspection activities undertaken**

– Inspection basis
  – Article 69, 72, 74 of the 『Pharmaceutical Affairs Act』, 『Rules on the Safety of Pharmaceuticals, etc.』 Article 48 and [Appendix 1] Pharmaceutical Manufacturing and Quality Control Standards
  – Regular pharmacist monitoring of completed drug manufacturers according to [Basic Plan for pharmaceuticals • Drug Production • Distribution Management in 2019]
– Inspection area
  – Workstation (production shop, packing shop)
  – Laboratory (biochemistry laboratory, microbiology laboratory)
  – Storage (Raw materials, materials, semi-finished products, finished products, returns, etc.)
  – Other manufacturing support facilities (air conditioning equipment, compressed air, purified water, etc.)

8. Inspection results, observations and deficiency

1)	**Quality management**	**Quality management**

Key checklist

□ Quality management

○ Quality management control (document number: QP-01, performed date: 2018.1.2)

– The manufacturing department and the quality department are operated independently and consisted of quality assurance team, quality control team and validation team under the head of quality (guarantee) department.

– The quality assurance team was responsible for matters concerning GMP document management and change management, deviance management and investigation, education training, self-inspection, supplier evaluation, product recovery, shipment review, and annual quality evaluation. The validation team was in charge of validation-related work, and quality management team was in charge of test management including quality testing and environmental monitoring of raw materials and products.

Deficiency

– None

2)	Premises & equipment	Premises & equipment (3)

Key checklist

□ Premise management

○ General

- It is a four-story building and uses the 2nd floor B zone, the 3rd floor, and the 4th floor B zone as a manufactory. It consisted of injection laboratories (separate separation of general preparations and anticancer injections) and quality control laboratory on 4th floor, content solidifying system laboratories on 3rd floor, raw material storage on 2nd floor, and completed product storage on 1st floor.
- The working area exposed to content solidifying system product was set to Grade D (Class 100,000), and the work area where external packaging was made was set to Grade E (unset area).
- In the workshops where the clean areas of all workplaces were changed, interlock systems were installed to prevent contamination. In the same clean class, the differential pressure was maintained at more than 5 Pascals, and when the clean class was changed, more than 15 Pascals.

△ Storage

○ General

- Raw materials related to content solidifying system, injectors are in raw material storage on 2nd floor, completed products are stored on 1st floor, and raw materials and completed product related to Cytotoxic anticancer agents are stored on 4th floor.
    - Raw materials related to Cytotoxic anticancer agents is warehoused following the waterway of raw materials, transferred to 4th floor through raw material forwarding room (E235) elevator.

○ Raw material receiving room (E235)

- No major change since last inspection, but insect repellent lamp location was moved to the test waiting room because of several reasons including the light of the insect repellent lamp attracting insects.

○ Raw material test waiting (E220)

- For the raw materials that are needed to be opened when measured with NIR analyzer, Raman analyzer was used for measurement.
    - Raw material SUGAR that was waiting to be received was measured with Raman analyzer, and the suitability was checked, and there was nothing significant to report.
    - The materials to be measured by NIR or Raman analyzer and materials to be measured in NIR clean booth are managed as a list of materials to be measured, and SUGAR materials that are waiting to be received are measured by Raman and the suitability was checked, among products waiting for receiving, and there was nothing significant to report.

○ Raw sample storage center (E218)

- Raw material reserved samples are stored following the storage conditions, two refrigerator (2~8℃), one freezer (-30℃~-20℃) were installed, temperature managed by CMS.

- Lists and registers of reserved samples were managed by entering in the LIMS system, and reserved samples were stored for 5 years since the amount of reserved samples is sufficient to perform more than twice as the number of prescribed tests.
  ※ The final packaging form of the main material of Dong-A Opalmon in the freezer was glass bottle and the reference specimen storage container in storage was PE. It was not possible to verify that the reference specimen storage material was equivalent to the final packaging material.

○ Raw material sample collection room (E216, Grade D)

- Raw material sample collection room and NIR room were separated, and clean booth of raw material sample collection room was operated 5 minutes prior to the work, and clean booth of NIR room was operated 30 minutes prior to the work.
  - Following the sample collection method (raw material) (document number: SOP-09B-2005), weighing booth of the sample collection room was regulated to warm up for 5 minutes
- Recent record of HEPA filter replacement of clean booth and PAO test result report were checked and PAO test were performed by the own company.
- Sample collection was performed using single use spoon, pipet and PE bags.

○ Raw material suitable storage room (E201)

- Raw materials which were judged to be suitable were classified and stored for each item after attaching the blue suitable label.
  - When raw materials were used, inventory and balance sheets were attached to manage inventory.
- Temperature and humidity were controlled through three thermo-humidifiers, managing temperature between 15~25℃, below RH 65%, and recorded 24 hours a day with central monitoring system (EMS) and temperature correction report was checked.
- Mapping test (including summer and winter) of storage room was processed, and maximum and minimum temperature and humidity were recorded three times a day by installing portable thermo-hygrometer at the worst spot.
- Based on the storage conditions, raw materials were stored in refrigerated storage room (E219), raw material dehumidification storage room (E207), and freezer, and were managed through central monitoring system (EMS).

  ※ Newly received raw material Spectra blend white were constructing Raman or NIR new data base, and it was stored in raw material suitable storage room without attaching confirmation inspection completed label since the program cannot print the confirmation inspection completed label while constructing new data. Related standard did not indicate detailed process of attaching confirmation inspection completed label when new raw material was received.

○ Completed product warehouse

- Products completed packaging process were transferred and stored in completed product storage room through 1st floor all rooms (A001) elevator, with test in progress label (yellow) attached, and suitable label was attached when it becomes test suitable status.
- Products that received shipment approval among domestic products were attached with shipment approval label (light green) and were all released to warehouse in Anseong.

- One thermometer connected with BMS was installed correcting sensor once a year, and attachment managing the test reports.

- Temperature and humidity are maintained with 4 air conditioners and 2 dehumidifiers without separate heating/air-conditioning equipment and managed with 3 calibrated thermo-hygrometers placed based on whether it is summer or winter, separated from BMS connected thermo-hygrometer.

- The location of thermo-hygrometers in winter and summer seasons were determined through mapping.

○ Packaged completed product storage (C351, Grade E)
- It is the storage location for anti-cancer agent related completed products that are packaging completed.
- Temperature and humidity are managed with separate conditioning equipment that runs 24 hours, maintained temperature being 19~25℃ and humidity being below 70%, monitoring through interlocking with BMS.
- Covered with colored nets to classify before and after the test.

△ Workstation

○ General details
- Put overshoes, hat, coat gown on in dressing room on 4th floor, undressing and changing into all-in-one and no-compensation in dressing room on 3rd floor, then entering solidifying system workstation.
- No record of Donga Opalmon related manufacturing facility and manufactory change was found, but patch-coating room (B114), store area (B143), weighing room (B142) among 3rd floor solidifying system workstation change was present and Mini Mixer, FBG, Solution Tank 400L, Dehumidification Air Conditioner for Fluidized Laminar, raw material waiting room (2), local circulating baghouse system were newly installed.

○ Raw material waiting room (B121)
- It is a workstation removing outer packaging remaining primary packing of received raw material, dust collecting booth was present and was run after 30 minutes of usage.
    - Record of HEPA and Bag filter change of dust collecting booth checked.
- Paper-wrapped raw material among received raw material were put into PE bag and was moved to workstations.

○ Weighing room (B128)
- Weighing booth was installed in the weighing room and was run 30 min prior to operation.
- Workstation, electronic scale, label printer, standard weights were installed in the weighing booth.
    - Standard weights were corrected every other year, and the record was checked.
- Electronic scale was checked daily through RWS, weigh and residual were managed through barcode system, weighing list was printed and attached to records, and was set calibration to be performed for every operation.
- Raw material with completed weighing were stored in semi-finished/drum weighing room (B135) after putting into double PE bad and drum container.

○ Liquid preparation chamber (B127)
- Liquid preparation tank was installed, and cleaning status was checked through attaching completed cleaning label.
    - Cleaning tank's CHT was set to 10 days.

○ Freeze dry room (B126)
- Freezer, freeze dryer were installed and freezer was washed by CIP.

○ Mixing chamber (B126)
- Mixer, local dust collector and more were installed.

○ Front room (C237)
- It was used as flow of human traffic when entering injectors workstation, and workers were entering through men's dressing room (2), women's dressing room (2), air shower after front room.

○ Raw material import room (C241, Grade D)
- This is where raw material that entered from storage through elevator are moving into workstation. Material were on standby after being transferred to material waiting room (2), and raw material were entered through raw material import room (1) (C211).

※ For the environmental management of clean areas, it was managed to maintain the differential pressure between cleanliness and regularly checked with differential pressure standard. Differential pressure of general injector hallway (C205, CNC) and raw material import room (C241, Area D) were recorded but real differential pressure was hallway (C205) and inner hallway (C242), and the differential pressure of the area where cleanliness change from CNC area to D area (between hallway and raw material import room) was unknown.

○ Men's dressing room (2) (C239, Grade D)
- To divide undressing location and dressing location, over bench was installed and managed.
- After undressing, passing over bench, disposable cap, up-and-down dust free garment, dust free shoes, mask were put on and entered through air shower.

○ Material waiting room (2) (C208, Grade D)
- Designated location for storing primary packaging material used in injector production.
- Material is stored on top of stainless palette, and rubber warfare, aluminum cap, vial and more are stored.

○ Dressing room (C210, Grade C)
- Dressing place when going into C area from D area hallway for medicine production. Gloves and overshoes were put on upon entering.

○ Preparation room (1) (C202, Grade D)
- Material and instrument containers were washed with injection water and dried. Complete test for sterilization filter before sterilization and completeness test for used sterilization filter were installed.

○ Laundry room (C22, Grade D)
- Location for washing working clothes and aseptic suit. 4 laundry machines were installed each two have designated purpose of use.

○ Distilled water manufacturing and PSG room
- Injection water storage tank and pure steam producing machine that are used for general injector production are installed.

  ※ Injection water room is in general injector workstation and managed with D rank cleanliness, but injector producing workers are doing both injection water room maintenance and aseptic workshop creation work, so could not exclude the possibility of workers entering aseptic workstation after high temperature work in injection water room.

○ Cleaning sterilization chamber (2) (C244, Grade D)
- HEPA filter installed clean booth is installed at where the instruments are being dried, HEPA filters are replaced when initial static pressure is twice as much, and once a year.

  ※ Environment management is performed through installing HEPA filter in clean booth and normal status of HEPA filter was checked through differential pressure gauge, but differential pressure of initial installation and differential pressure for replacement to properly perform checking normal range could not be checked.
- As a workstation to wash and sterilize ampule used for manufacture, ampule washer was installed and hot air over sterilizer and autoclave were installed in clean booth.
- Sterilized ampule was entered in asepsis hallway through pad box and transferred to ampule filling room.

○ Raw material carry-in room
- This is a place where raw materials standby before weighing, transferred to dispensary through pad box, and used as raw material residual, instrument transferred path.

○ Dispensary (2) (C224, Grade C)
- Workstation to weigh and dispensing raw material used for ampule production. Clean booth for weighing is installed.
- Raw material weighing takes place in HEPA-filter-installed clean booth, scale is checked with weights before usage, correcting them once a year.

○ Ampule filling room (C225, Grade B)
- Entered through asepsis undressing room (2) (C227, Grade C), asepsis washroom (2) (C228, Grade C), asepsis dressing room (2) (C229, Grade B), wearing disposable sterile work clothes, sterile work shoes, sterile gloves, and mask.
- As a secondary filtration and filling workstation of dispensed liquid, operation that product is exposed to workstation is managed to Grade A takes place inside of clean booth, and filling was installed inside.
- Instruments before filling, workers before usage are disinfected with bacterial excremented 70% ethanol and 70% IPA.

○ Packaging room (C247, Grade E)
- Carton packaging and box packaging after foreign object inspection.

○ Inspection room (2) (C250, Grade E)
- As a place where foreign object inspection and airtightness of charged capping ampule, 5 automated foreign object inspectors were installed.
- Foreign object inspectors were managed to measure intensity of illumination to be over 2000LUX, and alarm to go off if intensity of illumination is abnormal.

○ Semi-finished product storage (C256, Grade E)
- Designated and operated as a storage for semi-finished product and nonconforming items during process, storing semi-finished product based on the completion of foreign object inspection, managing temperature and humidity.
- Nonconforming items storing area are separately designated and managed.

○ General details (cytotoxic injectors workstation)
- Workstation of cytotoxic anticancer agents was installed on 4th floor of Dong-A ST.
- Air conditioning equipment used in the workstation of cytotoxic anticancer agents was used only for cytotoxic anticancer agents and exhausted through HEPA filter upon exhausting.
- Manufacturing water used to manufacture cytotoxic anticancer agents' injectors were separated from general material workstations.
- Workstation for cytotoxic anticancer agents' injectors was accessed through dedicated entrance through staircase.

○ Front room (C359)
- Entrance for anticancer agents' injectors workstation. Equipment to remove dust from the shoes upon entering was installed.
- Operated by installing key cards so that only authorized people can enter, and recorded entrance control record of outside visitors.
- Elevator was installed to use as raw material objects moving line that are used when manufacturing anticancer agents. Trap and insect repellent lamp were installed in front of the elevator.

○ Anti-cancer workplace (C359, Grade E)
- Raw material objects moving line that are used when manufacturing anticancer agents and human moving line are separated. Raw materials are transferred to raw material supply room (1) (C357) through anticancer workplace, and workers are entered through men's dressing room (2) (C356) and women's dressing room (2) (C355).
- Water facilities to wash hands were equipped.

○ Men's dressing room (C356, Grade E), Women's dressing room (C355, Grade E)
- To separate undressing area and dressing area, over bench was installed and managed.
- After undressed, passing over bench, workers checked in after wearing disposable hair cap, up-and-down dust free garment, dust free shoes and got rid of dust and foreign matters with roll cleaner.

- A full-length mirror was installed to check dress status.
- Shower booth was installed and operated to wash if stained with anticancer agents during packaging process, and working clothes collecting basket to collect working clothes when leaving the room.
- Entered to workstation with Grade E after changing work clothes.

○ Raw material import room (1) (C357, Grade E)
- Route that raw materials for anticancer agents' workplace use and carried through raw material import room (2) (C329).

○ Women's dressing room (1) (C324, Grade D), men's dressing room (1) (C325, Grade D)
- This is the location of undressing and changing when accessing Grade D area of anticancer agent injection, undressing clothes put on in men's dressing room (2) (C356) and change clothes when entering Grade D location.
- After undressing, wearing only underclothes, cross over bench and wear all-in-one dust free garment (hat included), dust free shoes (up to knees), and disposable mask, then disinfect hands to enter, and use roll cleaner to remove dust and foreign matters.
- Disinfecting fluid (clean call) are purchased, following the period of usage, and supplement when all of it is consumed.

○ Women's dressing room (1) (C323, Grade E), men's dressing room (1) (C326, Grade E)
- Exit through front shower room, shower room and dressing room upon exiting, and shower before exiting when product is exposed.

○ Raw material storage room
- Storage location of raw material used when manufacturing anticancer agent. Cabinets to store raw material needed to be stored in room temperature are installed, combination lock is used so that workers other than designated workers are not able to access and stored refrigerated or at a room temperature based on the storing requirements.
- Refrigerators are separated to identify raw materials that need to be kept refrigerated as waiting for test and suitable.
- Temperature and humidity are kept as 19~25℃, below RH 70% based on room temperature stored requirements, refrigerator are managed to stay 2~8℃ recorded 24 hours in central monitoring system, and the person in charge is reached through alarm system when it is deviant.
- Gemtabine HCL injection raw material that is main ingredient for Gemcit injection is checked.

○ Raw material storage room (real number C334, Grade D)
- Used as temporarily storing weighing completed anticancer agent raw material.

○ Waste waiting room (1) (C330, Grade D)
- Place to store waste from manufacturing anticancer agent, then discarded.

○ Detoxification washroom (C336, Grade D)
- Place of washing dust free garment that is used in Grade D area, primarily washed with top water, then washed with final injection water.

○ Sampling room (C335, Grade D)

- Raw material of cytotoxic anticancer agents is sample collected in glove box with ULPA filter, and leak test of the glove box is performed before use.
- Sample collection instruments and containers are disposed after one-time use.
- After sample collection of the raw material, waste is transferred through Pass box, and waste is put into a PE bag and wasted through detoxification washroom.
- Scale is installed in glove box and checked with weights before usage and corrected once a year.
- Store reserve samples of main material of cytotoxic anticancer agents and have refrigerator (2~8 ℃) to store main raw material used for requested items.

- Store twice as much of test quantity of reserve sample, and the primary packaging container is managed at the same or higher level as the packing state upon initial warehousing.

○ Preparation Wash Sterilization Room (C310, Grade D)

- Place to wash and sterilize instruments used to manufacture injectors, double door autoclave steam sterilizer was installed, and qualification assessment was performed once a year.
- Clean booth with HEPA filter was installed at where the instruments are washed, HEPA filter was replaced when static pressure is twice as the initial static pressure and replaced once a year.
- When washing instruments, injection water is used, neutral detergent (P3-COSA CIP90) is used as cleaning product and sterilized after packing inside of sterilized bag (HDPE Tyvek, disposable) before sterilization.
- Autoclave steam sterilizer cycle is accessed by a person in charge and stored in the program.
- Drain is disinfected once a month regularly, and the disinfectant (Deconex AF50) is bought.
- Completion test is performed on the filter before sterilization and the integrity tester is installed.

○ Instruments storage room (C309, Grade D)

- Place to store parts of manufacturing equipment after being washed, and hot water circulation dryer is installed.
- Used exclusively by product and stored by item and stored in storage box to prevent contamination.
- Manufacturing tank that is used to manufacture is checked.
- Parts of manufacturing equipment are washed before and after the use, and label is attached after being washed so that the washing status can be identified.

○ Detoxification room (C317, Grade D)

- Place to neutralize active ingredients before washing instruments used to manufacture and filling.

- 12%-Sodium Hypochlorite that is neutralizing agent is checked.
- Waste liquids that are neutralized are moved to waste disposal facility through vacuum pipe, then discarded.

○ Washing room (C318, Grade D)
- Storing neutralization completed parts, and washing neutralization completed parts.
- Check the integrity tester at the place where the completion of the sterilization filter is conducted.

○ Primary material storage room (C319, Grade D)
- Place to store primary packaging material used to manufacture anticancer injection agents.
- Materials are stored on top of palette made of stainless, rubber cap, aluminum cap, and more are checked.

○ Vial washing room (C315, Grade D)
- Workstation for vials that are used during manufacturing to be washed and sterilized, vial washer and vial tunnel sterilizer were installed.
- Injection water is used to wash vial, filter is installed for injection water and reclaimed water, and filter is replaced every time of use.
- HEPA filter in the tunnel sterilizer was replaced when static pressure is twice as the initial static pressure or every year.
- A device is installed at the end of the tunnel sterilizer to check floating particles in real time. A differential pressure gauge is installed to check the differential pressure between the filling room and the tunnel sterilizer.
- Vials sterilized in the tunnel sterilizer is transferred to the filling in sterile filling room.

○ Manufacturing room
- Accessed after going through manufacturing undressing washing room (C313, Grade D) and manufacture dressing room (C312, Grade C) and change into Grade C outfit. Grade C outfit is over gown a disposable dust free garment, over shoes, cap, gloves and mask with filter.
- Pass box to take in weighted raw material and take out used instruments is installed.
- Workstation to scale and manufacture raw material, glove box and clean booth for weighing is installed, glove box weighing main material and leak test is performed before use.
- Two scales are installed in clean box, filler was measured, and maintaining scale is performed as before use and correcting once a year. Weights used for maintaining is corrected externally every year.
- Raw material scaling is performed in glove box with ULPA filter, installing scale inside, checking with weights and correcting once a year.
- Nitrogen pipes are installed for nitrogen filling during preparation and sterilization filters are installed at the end use point. They are replaced every six months, and completeness test is performed before and after the replacement.

- After preparing it in the preparation tank, filter it with the excess fluid bag through the transfer passage to the filling room.

○ Sterile filling room
- Need to be entered through undressing room (C305, Grade C), sterile front dressing room (C304, Grade C), sterile dressing room (C303, Grade B), disposable sterile work clothes, sterile gloves, and mask need to be wore.
- When exiting, need to go through sterile front undressing room (C305, Grade B), undressing room (C307, Grade C), dressing room (C308, Grade C).
- Workstation of filtering and filling manufactured liquid. Work that the product is exposed is performed inside of O-RABS and managed as Grade A, and liquid filling, camping machine and P&S Disk Inspector was installed.
- The filling of manufactured liquid is installed in the SART by installing the filter input port GAMMASART ATD from the preparation room and connecting the hose to filter it using the transfer pump (quantitative pump).
- Instruments before filling and gloves of O-RABS are disinfected with germ-free 70% ethanol or isopropanol.
- Location of filling and capping have real time floating particle monitoring system installed, monitoring floating particles since putting parts together. When performing sterilization work, measuring floating particles and drop bacteria, and performing surface bacteria of instruments and workers after work is performed.
- Movable clean booth was used to prevent contamination of the product.
- The semi-finished product that has been charged is automatically loaded into the freeze dryer using the conveyor belt. For products that have completed the freeze-drying process, the operator was unloading them and transporting them to the next process using the conveyor belt.
- Nitrogen supplied through germ filter after freeze-drying process is completed.

  ※ Process to check quality of the sterilized rubber cap produced during anticancer agent production that goes through Grade B area to filling machine Grade A area without contamination and microbiological contamination prevention process need to be created.

○ Cap sealing and vial external washing room (C302, Grade B)
- External washing place for vial with completed filling, and vial external washing machine was installed.
- Injection water was used as washing liquid.

○ Freeze-drying machine room (C348, Grade E)
- One freeze-drying machine was installed, and detoxification tank to detox wastewater from cytotoxic anticancer agents' workstation was installed.

○ PSG & WFI room (C350, Grade E)
- Injection water used for anticancer agent production storage tank and manufacturing equipment that manufacture pure steam was installed.

○ Anticancer agent packing room (C317, Grade E)
- After anticancer agent filling and vial surface wash, reviewing of surface damage and filling amount check are performed and carton packaging and box packaging is performed.

○ Foreign object inspection room
- Place to perform foreign object inspection of charged vials. Six foreign object inspection machines are installed, intensity of illumination set as over 1000LUX before operation, and illuminometer being corrected once a year.

○ Packing waiting room (C344, Grade E)
- Place to store semi-finished products before packaging completed products.
- Temperature and humidity are controlled by operating separate conditioning equipment 24 hours, temperature being 19~25℃, humidity being below 70%, and monitored by interlocking with BMS.
- Covering with nets with colors are used as a method to identify before and after the test.

○ Packing material waiting room (C338, Grade E)
- Place to store secondary packing material.

○ Grounding room (C360, Grade E)
- A grounding device was installed as a place to ground the manual and was kept warm and well-maintained during the manual was stored.

○ Washing room (2) (C347, Grade E)
- As a place to wash working clothes of Grade E, washing machine was installed.

△ Laboratory

○ General details
- Quality control laboratory was in 4th floor of Cheonan factory of Dong-A ST, divided into biochemistry laboratory, instrument analysis laboratory, stability test laboratory, and microbiology laboratory.
- All of laboratory of quality control laboratory's temperature and humidity are controlled as 19~25℃, below 70%, taking moves when managed to be 20~24℃, below 65%, which is an Alert Level, connected to EMS.
- All of instruments in quality control laboratory was managed by providing test instruments management number, indicating inspection dates and next inspection date.
- When test was requested in production part, relevant contents were submitted, QA department being in charge of sample collection, and collected samples were handed over to QC department.
- Test process was managed by using LIMS, performed in an order of request test → test submitted → order test → sample collection (QA) → write test request form and sample transfer (QA) → QC submission → sample distribution → test distribution for each part → perform test → entering test results to LIMS → heads of each parts mid-review → chief confirmation (QC suitable) → QA review → review related document and shipment approval (quality department chief approval).

○ Standardized goods storing room (G706)

- Standardized goods storing room was managed with air conditioning and air conditioner, having 8 standardized goods storing chamber, kept in room temperature (1~30℃), refrigerating (2~8℃), freezing (-15~25℃) based on standardized goods' storage requirements.
- Storing chamber managed with connecting CMS, alarm system going off when temperature is deviant, managed with printing recording paper in a regular basis.
- Standardized goods management register of 'Gemcithavin hydrochloride' related to Gemcit injection was checked.
- Use period of standardized goods were followed by the use period determined by the manufacturer, in case of absolute standardized product, the manufacturing number and validity were checked at each site, and check list was written.

○ Biochemistry laboratory 3 (G705)

- The equipment used for the enzyme test was equipped and was conducting the test that required the shading.
- Potentiometer titrator used for potentiometric titration was installed.

○ Biochemistry laboratory 2 (G704)

- Dryers and decompression dryers used for drying loss test, 2 TOCs, automatic specific gravity measuring instrument, refractometer and 2 UVs were installed.
- Dryers and decompression dryers were inspected every 3 months and stopwatch to measure time was corrected every two years.
- TOC was checked with standard solution every three months and externally checked every year. TOC sample bottles were one-time use.
- Self-checked UV every six months and qualification evaluation was performed every year externally.
- pH, the conductivity meter was checked daily with a standard solution and retested with a suitable standard solution for each test.
- pH meter was used by corrected as 4.01, 7.01, 10.00 and correcting solution use period was set as three months after opening.

○ Biochemistry laboratory 1 (G707)

- Potentiometric titrators, melting point meters, insoluble matter testers, non-photometric meters, incinerators, moisture meters, wear and tear gauges, particle size analyzers, and disintegration testers were installed.
- Potentiometric titrators, melting point meters, non-photometric meters were Inspected by an external manufacturer.
- For disintegration tester, temperature, time, and operation condition were checked every month.
- A gas tightness tester used for the airtightness test was used to check the decompression using 0.1% -methylene blue solution by setting the decompression standard and time. It was confirmed that the timer (2 years) and the pressure gauge (1 year) used in the test were corrected.
- Melting point tester was using standard materials (benzoic acid, saccharin) for testing.

- The particle size analyzer for the particle size analysis of raw materials was a device that can be tested by dry and wet methods.
- The roughness was measured at the measurement position by using an illuminometer for an insoluble water tester. The illuminometer was calibrated once a year, and the director of illuminance management was confirmed.
- The incinerator used for the ignition residue test was able to heat up to 1000 ℃, and the qualification test and the temperature sensor calibration were carried out every year.
- The thin plate and development tank of the thin layer chromatography (TLC) used for the identification test were confirmed, and Auto TLC was used.
- Ultrapure water maker was installed, and the filter was replaced once a year.
- 4 Hume Hood that are used for dangerous test was installed used during tests.
- 9 scales used for test were installed and used, Daily inspection, weekly inspection, monthly inspection and quarterly inspection were carried out by the company, and annual inspection was carried out by an external organization. The weight used for the inspection was carried out external calibration once a year.

○ Weighing room (G708)

- 8 scales were installed, method of management was same as biochemistry laboratory 1 (G707) and usage history was recorded.

○ Instrument analysis laboratory 1 (G709), instrument analysis laboratory 2 (G718), stability test laboratory (G773)

- Analysis instruments were installed in instrument analysis laboratory 1, instrument analysis laboratory 2, and stability test laboratory, and HPLC (UPLC included), GC (Head Space), AAS, IC, GC/MA, ICP were operated.
- Instrument analysis laboratory 1 and instrument analysis laboratory were performing test for raw material and products, and stability test laboratory were performing test related to stability test.
- Internally saved data for GC and HPLC related to Gemcit injection was checked, and test record of instrument usage log and column usage log were checked.
- The mobile phase used for the test was prepared by using a preparative preparation (no more than 24 hours), and the instrument and column cleaning solvent were set to the expiration date for 7 days.
- For each item to apply HPLC, a dedicated column was used, and the column was managed using LIMS and printed and stored once a month.
- For the gas used for GC and AAS (N2, H2, high-purity air, He, O2, Ar, N2O, C2H2), gas piping was installed and transferred from the outside gas chamber to the inside, and the direction and components were marked on the gas piping.
- Detector of GC (FID, ECD, TCD) and detector of HPLC (UV, RI, FL) were checked.
- Self-inspection for GC, HPLC, AAS, ICP were performed twice a year, and were inspected by an external manufacturer once a year.
- Checked Cathode Lamp (Pb, Zn, Ni, Hg) of AAS was confirmed, additional equipment used for cold vapor analysis of mercury analysis was identified.

○ IR room (G710)
- 1 FT-IR is installed, and ATR used for testing and facilities for making KBr and disks used for potassium bromide purification were identified.
- FT-IR was inspected by an external manufacturer once a year.
- LC/MS/MS was installed and was in use.

○ Anticancer agent pretreatment lab (G720)
- Laboratory performing pretreatment of anticancer agent raw material and manufacturing test, entered through dressing room and undressing room wearing disposable all-in-one work clothes, mask, gloves and goggles.
- pH meter and Karl Fischer moisture meter, standardized product refrigerator (2~8 ℃) and freezer (-25~-15 ℃) were installed, temperature monitored for 24 hours.
- After the test, it was washed first with antidote before washing, and was discarded once a week using a wastewater bottle.

○ Elution test room (GG716)
- Twelve dissolution testers were installed, and qualification test for the dissolution tester was performed externally once a year and checked every time it was used.

○ Reagent storage (G715)
- Distinguished into 6 categories by refrigerating (2~8℃), freezing (-15~25 ℃), room temperature (15~15 ℃), solid reagent, narcotics and strong acids and bases, each was stored in a reagent chamber, temperature was managed with CMS.
- LIMS was used to manage a list of reagents.
- Reagents were categorized into opened reagents and unopened reagents, separately categorizing solid reagents and liquid reagents.
- The storage conditions and expiration date for reagents shall be in accordance with the test report enclosed with the purchase. Unless otherwise specified in the test report, room temperature storage conditions are set to 5 years from the date of receipt (3 years after opening) and 3 years from the date of receipt (2 years after opening) for refrigerated and frozen reagents.

○ Material testing room (G797)
- Material testing room was operated on the 4th floor separated from biochemistry laboratories.
- The standard test of the primary material and the standard and label of the secondary material (external packaging, sticker, insert paper) were being tested.
- Introduced the EYE-C QC system and tested the printed contents by comparison with the standard sample using a computer program.
- NIR was placed for material testing use and inspected by an external manufacturer twice a year.

○ Microbiology lab overview
- Microbiology lab and microbiology limit lab were divided and operated as Grade C, and each has BSC (Bio Safety Cabinet) operated as Grade A.
- Incubation room (G763), badge preparation room (G757), pretreatment room were operated as Grade D, and need to enter through reception hall (G750), undressing room (G751, G753), dressing room (G752, G754), putting two piece dust free garment, dust free shoes, and disinfecting hands.

- In the area where the cleanliness is changed, a differential pressure gauge was installed to check the flow of the differential pressure, and when the cleanliness was changed, the differential pressure was managed to be 1.5mmAq or more and 0.5mmAq for the same cleanness.

○ General test laboratory (G716, Grade D)
- Insoluble particulate tester and balancing tester were installed.
- Insoluble particulate tester was installed in BSC that is managed as A supply and inspected by an external manufacturer once a year.
- Bacterial identification was performed on bacteria detected above Grade C grade and trend analysis was performed.

○ Activity test room (G762, Grade D)
- Endotoxin test heating block and endotoxin test device (UV Reader) were installed.
- The heating block temperature sensor and the micro pipette were calibrated once a year. And it was confirmed that the tip used in the endotoxin test was a product without endotoxin interference.

○ Incubation room (G763, Grade D)
- Seven incubators are installed, and each is used for aseptic test, microbial limit test, water test, medium filling test, environmental test and E. coli test.
- Temperature of incubators is recorded 24 hours and have alarm system.
- High pressure steam sterilizer used for sterilization of waste media was installed.
- In the microbial limit test room (G768, Grade C) where the microbial limit test is carried out, a pass box for carrying test tools was installed, and the lamp inside the pass box was replaced every three months.

○ Badge preparation room (G757, Grade D)
- Fridge and freezer where preparation of badge and storing badge and reagents and dry heat sterilizer (250℃, 40 min) for sterilize the instrument used for endotoxin test is installed.
- The badge is dispensed and used immediately before the test. Each time a badge was prepared, a unique number was assigned, and a badge performance test was conducted.
- Prepared badge can be used for 3 weeks and verification of the period of use is performed.
- LAL reagents, LAL water, LAL standards are stored in freezer (-25~-15℃) and reference stain is stored in fridge (2~8℃), badge storing chamber is kept as 20±2℃, monitored 24 hours and has alarm system.

○ Sterilization wash room (G764, Grade D)
- Clean booth with HEPA filter is in area of washing, and autoclave steam sterilizer was installed.
- The autoclave was sterilized with badge, sterile clothing, and vinegar, and a sterile loading pattern was attached. After sterilization, it was opened and taken out from the other side of the sterile laboratory.

- Water bath used for badge production and washing machine to wash work clothes were installed. Sterilized clothes were washed daily, and other work clothes were washed once a week.
- Pass box was installed to bring test tools into a sterile laboratory (G772, Grade C) where sterile testing.

○ Sterile laboratory (G772, Grade C)
- Laboratory where sterile testing is performed, and accessed through undressing room (G765), washing room (G766), dressing room (G771), wearing sterilized work clothes (bandana, all-in-one dust free garment, overshoes, gloves, goggles, mask).
- BSC that are managed as Grade A was installed.
- A canister was used during the sterility test, and there was a canister pump inside the BSC.
- Sterile laboratory was performing fumigation using hydrogen peroxide quarterly.

○ Microbial limit laboratory (G768, Grade C)
- The laboratory where the microbial limit test is conducted, and the entrance procedure and structure are the same as sterile laboratory, and the BSC managed by Grade A was installed.

○ Product storage warehouse (G723)
- Temperature are managed to be 15~25℃, below RH70%, monitored 24 hours through central monitoring system (EMS), and maximum and minimum temperature and humidity are recorded by placing three portable thermo-hygrometers.
- Samples are stored be capable of performing at least two times the prescribed tests, packaged in the same form, the shelf life was stored for an expiration date plus one year. Archived samples and reference samples were stored separately.
- Refrigerated (2~8℃) and cold (1~15℃) chambers were installed.

○ Constant temperature and humidity room 1, 2 (G736, G782)
- Long-term storage and acceleration chambers, harsh chambers, refrigeration chambers, translucent chamber chambers, and export stability chambers were installed.
- The long-term stability test condition was 25±2℃, RH 60±5%, which was managed by installing a thermo-hygrostat.
- Post-marketing stability test specimen for Gem sheet stock has been checked.
- Chambers are all monitored by central monitoring system (CMS) 24 hours and managed to send email or cell phone alarm if deviant.

□ Air conditioning equipment

○ Air conditioning facility
- Private use of air conditioning equipment facility was installed in 4th floor of manufacturing building for general injector building, and 7 air-conditioning units (AHU #1, #2, #4, #6, #11, #18, #22) were operated related to general injectors.
- No facility change history after last inspection

- AHU#1: outside air → outside air filter → free filter → cooling coil → heating coil → medium filter → HEPA filter → HEPA filter of B area workstation → workstation → return
- AHU#1: outside air → outside air filter → free filter → cooling coil → heating coil → medium filter → HEPA filter of C area and D area workstation → workstation → return
- A total of 9 air-conditioning units (AHU #10, 12, 13, 14, 15, 16, 17, 19, 22) were operated in relation to the solid-state workstation.
    - Monthly inspection record of AHU #9, 10 were checked, differential pressure and replacement history of each filter was checked and managed record, and nothing significant to report
- For daily inspection, the air filter pollution degree, air conditioner leak, each filter differential pressure was recorded and managed, and the recent daily inspection table was confirmed.
- Air filter was replaced monthly, prefilter was replaced quarterly, medium was replaced yearly, HEPA filter was replaced once in three years.
    - Medium and HEPA filter replacement record around March 2018 was confirmed and after replacing the HEPA filter, self-integrity test was conducted and recorded the results.

○ Air Conditioning System Preventive Maintenance Management

- Document number: SOP-06A-1002, confirmed date 2017.5.12.
- Daily and monthly inspections and semi-annual inspection items and procedures for air conditioners, and measures to be taken in case of abnormalities are specified.
- Air filter was replaced monthly, free filter was replaced every three months, medium filter is replaced either monthly or if double initial differential pressure, HEPA filter was replaced either every three years or if double initial differential pressure, and completeness test was performed every year.
- A differential pressure gauge was installed to check the pressure before and after the filter, and self-calibration was performed every year.

□ Pneumatic test

○ Items to be confirmed

- General compressed air and oil free type compressed air equipment are independent, general compressed air is used to operate the equipment, and some are also supplied by Dong-A Pharmaceutical, and Dong-A ST was using only oil-free type compressed air in the workshop.
    - There were 5 oil free equipment.
- General compressed air: air storage tank → final chiller → water separator → air filter 5㎛ → cooling dryer → adsorption dryer → air filter 1㎛ → air filter 0.01㎛ → use
- Oil free compressed air: air storage tank → final chiller → water separator → air filter 5㎛ → cooling dryer → adsorption dryer → air filter 1㎛ → air filter 0.01㎛ → use

- No change after the previous inspection, regarding maintenance and management, related records such as daily inspection log and filter replacement history were checked.
    - Daily inspections such as temperature, pressure, and operating hours of the equipment to be operated and consumable replacement cycles, cooling water and air leaks are performed monthly. There was a recent inspection record and there were no specifics.

○ Compressed air system operation (Oil free) (Document number: SOP-05C-0011, Enforcement date: 2017.6.1)

- The overall procedure for operating compressed air system was specified.

□ Manufacturing water

○ Manufacturing water system

- Top water was used as raw water.
- The purified water production apparatus is manufactured in the purified water production facility on the first floor of the manufacturing building, the purified water is transferred through pipes from content solidifying system building to anticancer injection building. The transferred and stored purified water is used to produce used water and pure steam.
- Changes: In the past, the purified water transferred through pipes from the Dong-A Pharmaceutical purified water tank was managed in a 2-2 loop. This change was made to 1-4 Loop by connecting to Dong-A ST purified water system instead of Dong-A Pharmaceutical. Newly installed three purified water points (56, 57, 58) and one injection water point (64).
    - Change management number 20180219-1, change confirmation date 2018.2.27. Completion of change document confirmation date 2018.6.8.
    - Purified water piping diagram, system diagram change, injection water piping diagram change, related standard revision, requalification evaluation performed.

○ Purified Water Production and Distribution System

- Purified water production system: top water storage tank (300 Ton) → top water auxiliary tank (10ton) → Circulation Pump → Automatic multimedia filter (Gravel/Sand/Activated Carbon) → Automatic Softener (Cation Exchange Resin) → Cartridges filter (10㎛) → Softened Water Tank (1Ton) → Pressurized Pump → Cartridge Filter (6㎛) → Pressurized Pump → R/O System (5.5m3/hr) → EDI System (5m3/hr) → UV Lamp → Purified water storage tank (15Ton) → Circulation Pump → UV Lamp → Distribution device (separated as content solidifying system building and anticancer injection building) → purified water storage tank (15Ton) circulation.
- Purified water circulation system (1-2 Loop): 1st floor purified water production System → purified water storage tank (3Ton) → Circulation Pump → UV Lamp → heat transmitter → point of use → purified water storage tank (3Ton)
- Purified water circulation system (1-3 Loop): 1-2 Loop → purified water storage tank (6Ton) → Circulation Pump → heat transmitter → point of use → purified water storage tank (6Ton)
- Purified water circulation system (1-4 Loop): 1st floor purified water production system → purified water storage tank (5Ton) → Circulation Pump → heat transmitter → point of use → purified water storage tank (5Ton)

○ Purified water production and distribution system maintenance

- Maintenance was carried out according to the Purification Water System Prevention and Management Guide (document number SOP-04B-0003) and Purification Water System Management Guide (document number SOP-04B-0002).
- Regular inspections were carried out once a month, and the filter replacement cycle and replacement method, UV lamp replacement cycle, instrument calibration management, cleaning and hot water sterilization cycle and procedures were specified.
- Micro filters were replaced once a month, and RO membranes and EDI modules were replaced when performance was deteriorated based on monitoring results such as conductivity.
- UV lamps were replaced every 11 months and vent filters were replaced before every 6 months of hot water disinfection.
- Chemical cleaning was performed by using NaOH, Na, EDTA, HCl, H2O2, hot water disinfection and passivation were performed every 6 months.
- Injection water production system (1-1): 1st floor purified water distribution line → WFI Generator (distilled water, operated as 140℃ → injection water storage tank (3T) → heat transmitter → point of use distribution line → injection water storage tank (3T) (circulation)
- Pure Steam production: 1st floor purified water distribution line → Sub tank → heat transmitter → PSG → point of use

○ Manufacturing water quality control

- In Top Water Management Guide (document number SOP-04C-0001, confirmation date 2017.06.12), Samples were collected twice a year at the supply point and once a year at the point of use, and quality inspections were conducted according to drinking water management standards.
    - Water test was commissioned to Cheonan-si Clear Water Office.
- Quality inspection is conducted once a month for the designated point of use according to the purified water management regulations. Quality inspections were conducted every day on supply and circulation points, and online monitoring of conductivity, TOC, etc.
    - Test categories: property, pH, conductivity, total organic carbon, general bacterial count
    - The company set and controlled warning and action levels and defined and operated procedures for exceeding these standards. If the warning level was exceeded for three consecutive times, it was regarded as exceeding the action level.
- In the second half of 2018, the purified water trend analysis report (document number TAR-Q5-PW-053, confirmation date 2019.1.29) was confirmed, and no deviation exceeding the action level and warning level occurred for all test items.

○ Injection water quality control

- Quality inspections were conducted once a week at designated points of use, and daily quality inspections were conducted at supply and circulation points based on injection water management guide (document number SOP-04A-0001, confirmation date 2019.3.20) and Pure Steam management guide (document number SOP-04A-0003).
    - After the CIP and SIP, the quality test was conducted on all the points before the loop, and the online monitoring of conductivity, TOC (anticancer workstation only) was conducted.

- Test categories: property, pH, conductivity, total organic carbon, general bacterial count, endotoxin test
- The company set and controlled warning and action levels and defined and operated procedures for exceeding these standards. If the warning level was exceeded for three consecutive times, it was regarded as exceeding the action level.

– In the second half of 2018, the injection water trend analysis report) for workplace injections (document number TAR-Q5-WI-029) and the anticancer workplace injection water trend (document number TAR-Q5-WI-028) was confirmed, and no deviation occurred.
  - Standard and test method: pH (self-standard), conductivity (USP), general bacterial count (USP, JP), TOC (USP), endotoxin (KP)

□ Management of automation equipment

○ Calibration Management Standard
– Document number SOP-06E-0001, confirmation date 2017.12.7)
– An annual calibration plan was prepared and regularly calibrated, and a list of instruments for internal and external calibration was prepared and performed within the next inspection month once a year.
– In case of external correction, a national accredited calibration institution was selected and commissioned. At the completion of the calibration, a calibration report and a calibration label were prepared and managed.

□ Environment management
○ Environment monitoring measurement method and management standard
– Document number SOP-05A-0001, confirmation date 2019.3.25.
– For each cleanliness, test items, test cycles, test procedures and test criteria, sample collection volume, warning level, and handling procedures in case of deviations from the action level were specified.
– Zone A conducts the test of falling bacteria, suspended bacteria, surface bacteria, and suspended particles twice a month. In addition, the operator tested the surface bacteria once a year.
– Zone C conducts monthly test of drop bacteria, floating bacteria, surface bacteria, and suspended particles. Zone D was tested once a quarter on falling bacteria, suspended bacteria, surface bacteria, and suspended particles.
– Test standard was managed by applying EP, Alert levels and action levels were set and managed separately.

○ Management criteria for environmental monitoring during injection work
– Document number SOP-05-0007, confirmation date 2019.3.21.
– It defines the environmental monitoring measurement items and measurement cycles, used badge and culture conditions, and cleanliness test standards when injection work.

※ In the case of the drop bacillus test, the test was conducted in the morning and afternoon separately (about 1 hour and 30 minutes) during the working hours, but it is necessary to carry
out the test by continuously exposing up to 4 hours including lunch time. In the case of worker surface bacteria, only one of the workers was tested, but it was necessary to test the surface bacteria for all possible workers.

○ Environmental Monitoring Trend Analysis Report

– Second half of 2018 Grade A area trend analysis report
  - Document number TAR-Q5-EM-040, confirmation date 2019.1.21.
  - Trend analysis was conducted every half year.
  - Environmental monitoring was conducted twice a month for clean booth and O-Rabs in the sterile workplace for injections. Suitable for all times in question.

– Second half of 2018 Grade B area trend analysis report
  - Document number TAR-Q5-EM-050, confirmation date 2019.1.21.
  - Trend analysis was conducted every half year.
  - The results were analyzed by monitoring the environment twice a month at regular and non-working times for the injection-free workplace and microbial laboratory. Suitable for all times in question.
  -

– Second half of 2018 Grade C area trend analysis report
  - Document number TAR-Q5-EM-041, confirmation date 2019.1.31
  - Trend analysis was conducted every half year.
  - Environmental monitoring was conducted on a monthly basis for the manufacturing room, aseptic undressing room, front room, microbiology laboratory, and raw material storage in the injection workplace.

○ Environmental monitoring measures and management standards for anticancer workplaces (SOP-05A-0012, 10, 2019.04.01.) and environmental monitoring control standards for anticancer work (SOP-05A-0017, 16, 2019.03.18.)

– Clean grade and frequency

Section	Drop Bacteria	Floating Bacteria	Floating Particles	Surface Bacteria (facility)
Grade A	Twice a month	Twice a month	Twice a month	Twice a month
Grade B	Twice a month	Twice a month	Twice a month	Twice a month
Grade C	Monthly	Monthly	Monthly	Monthly
Grade D	Quarterly	Quarterly	Quarterly	Quarterly

○ Environmental monitoring trend assessment data (anticancer agent building)

– Fist half (TAR-Q5_EM-039, 19) and second half (TAR-Q5-EM-039, 20) of 2018 trend analysis data
  - Assessment has been conducted on the clean zone of anticancer agent building Grade A, B, C, D area.
  - Assessment period: first half (2018.01. ~05), second half (2018.07~12)
  - Assessment categories: assessment on floating particles, floating bacteria, drop bacteria, facility surface bacteria.
  - Assessment result: No results exceeded the standard values for the first half and second half of 2018, and the environmental monitoring results for the workplace were appropriate.
  - Alert Level and Action Level was set and managed for floating particle and floating bacteria, drop bacteria, surface bacteria.

□ Content solidifying system workplace checklist

○ Workplace overview

- Content solidifying system work area was in 3rd floor of manufacturing building, largely divided into weighing-coating area and packing area.
- Thermo-hygrometer and temperature humidity censor (EMS) were installed in workplace, managed to have temperature 19~25℃, and humidity below 60%.
- The differential pressure system was installed in the cleanness change area and dust generation area. The differential pressure was recorded every hour of the operation time. In other places where the differential pressure system was not installed, the differential pressure was checked • recorded periodically once every six months.

○ Visitor entrance (Grade E)

- Entrance of workers and visitors were separated, male workers entering through 4th floor undressing • dressing room and female workers entering through 3rd floor undressing • dressing room.
- After getting rid of foreign substance with shoe vacuum, wearing bandana, gown, overshoes, entered to manufactory through washing facility and air shower.

○ secondary undressing and dressing room (male: B133, female: B001, grade D)

- After undressing Grade E outfit, all in one work clothes and mask were worn.
- Over bench was installed inside and washing facility and hand sanitizer were installed.
- Hand sterilizers are using off-the-shelf products and have been marked with expiration dates and replacement dates.

○ Front room (B140)

- This is the place where raw materials from the elevator are brought in.
- Roll up door was installed in front and back of the front room, operated with interlock equipment.

○ Raw material waiting room 2 (B121)

- It corresponded to the removal of foreign substances on the imported outer packaging and the waiting area before manufacturing.
- There was a return waiting area and a weighing waiting area.
- Local dust collector, temperature sensor (EMS) and differential pressure gauge were installed

○ Weighing room (B128)

- Weighing booth was installed inside of weighing room, operated an hour prior to work.
- Inside of weighing booth, there were worktable and 2 electronic scale, label printer, standard weights were installed.
- Weighing and balance management was carried out through RWS and bar code system, and it was set to print out weighing list, attach to record, and perform calibration every time.
- Cleaning was done before and after every weighing operation and water cleaning is performed on the prefilter upon completion of work.
- The weighed raw materials were stored in semi-finished / drum waiting rooms in double PE bags and drum containers.

○ Fluid bed granulation chamber 2 (B056)
- 4 preparation tanks, fluid bed granulation chamber, thermostat, and sizing machine were installed.
- There was a scale for re-weighing subdivided raw materials, the preparation of binder solution, granulation, and formulation were carried out.
- The agitation time, speed and temperature were checked for the preparation tank, and regular calibration was carried out through the facility guarantee team.
- Fluid bed dryer drying cloth was used exclusively for items

○ Mixing chamber 5 (B065)
- Empty mixer, local dust collector, and electronic balance were installed.

○ Tableting room 8 (B057)
- Tableting machine, drum mounting lift, electronic scale was installed.
- Tablet testing system, a debrancher and a metal detector were used together.
- Work was carried out after test tableting. Metal detectors were used after testing as standard materials before use.
- Mixed semi-finished product was injected into tablet press through dedicated transfer pipe.

○ Coating machine manufacturing room 1 (B042)
- Place of weighing coating base, distilled water and organic solvent.

○ Coating room 1 (B307)
- The solution tank and coating machine for preparing the coating solution were installed.

○ Automatic inspection room 3 (B137)
- An automatic tester was installed, and the entire test was conducted by checking the top, bottom, left, and right sides based on the standard model values.

○ Parts storage room 3 (B130)
- Weighing scoop storage was installed.
- Washed scoop was stored in PE bag, managed by attaching label on outside of PE bag indicating washing date, washing expiration date.
- In addition to the scoop, fluid bed dryers and sieves (screen, mesh) were also stored.

○ Parts storage room (B022)
- This is where the punch of tablets is stored. The punch is stored in each cabinet and each item name is clearly marked.
- The punches of Stillen tablets were confirmed, and drawings were managed for each punch.

○ Process laboratory (1) (B017)
- This is where LOD values of granules are measured during the IPC test.

○ Process laboratory (2) (B116)
- Place to test tablet without coating's IPC.
- Instruments for testing hardness, disintegration, and wear and tear, electronic scales and sieves for testing weight, thickness and diameter were installed.

○ Semi-finished/drum waiting room (B135)
- The semi-finished product was mixed in PE bag and stored in SUS drum container before mixing~packing.
- Managed to maintain 15~25℃, below 60% and recorded 24 hours by central monitoring system (EMS).
- The non-conforming storage was partitioned, and a locker was installed.
- The status of semi-finished products (appropriate / not appropriate, test in progress, etc.) was controlled by the color of the nets connecting the same lots.
- A separate booth for sample collection of semi-finished products was in operation.

○ Parts washing room 1 (B032)
- Non-separable instruments are to be cleaned in the relevant workshop and are the places to clean removable parts and exhaust filters.
- The drain was disinfected once a month.
- Cleaning racks, cleaning tools and washer (unused) were installed and cleaned parts were stored in the parts compartment.

○ Semi-finished product storage room (D361)
- It is a place to store the semi-finished product which has been tested after the coating process until it is judged to be suitable, and managed to stay 15~25℃, below 60% and recorded 24 hours with central monitoring system (EMS).
- Scale to check the acquisition volume for semi-finished products was present.

○ Material storage room (D366)
- Primary and secondary material were stored on top of metal pallet.
- Temperature and humidity managed to be 19~25℃, below 70%.
- When importing into the material storage room, the quantity and appropriate label of the material were checked and brought in, and the remaining amount after the production was discarded (including unprinted materials).

○ Bottling room 3 (D399)
- In the bottle packing room, worker entrance (a change room) and a raw material entrance were separated, and an interlock and a differential pressure gauge were installed.
- Bottle sorting machine, bottle inspector, silica gel dispenser, counter, bottle filling machine were installed.

– The bottle packing line was connected across the bottle packing room (area D) and the secondary packing room (2) (area E), where the differential pressure was measured every hour.

○ Secondary packaging room 2 (D312)
– Managed as Grade E (temperature and humidity management, Environmental monitoring not carried out, use air conditioning same and equivalent as class D).
– Storage box for storing materials (label, manual) of work product was installed.
– Secondary packaging machines such as cartoners and labelers were installed.

※ Bottling & Secondary Packaging Line
Bottle sorter → Bottle → Bottle checker → Silica gel input → Pharmaceutical input and counting → Capping and Inspection → (area E) Labeling → VISION inspection → Weight check → Barcode and Date Printing → Carton packing

○ Product storage warehouse (E301)
– Place where finished products are stored. Completed Stillen tablet product was confirmed.
– After replacing the pallets through the product receiving room (D342), the finished products were transferred to the product storage warehouse.
– Temperature was managed as 15~25℃, and humidity was managed as below 80%. Mapping test (including summer and winter season) was carried out and a portable thermo-hygrometer was installed at the lowest point to record maximum • minimum temperature and humidity three times a day.
– The person who entered the room was entered with a card and checked the straps and insect catcher.
– Unsuitable storage was separated, and lockers were installed.
– There was a separate refrigerated products storage.

Deficiency

□ The following items should be supplemented with regard to environmental management (general injection).

○ For the environmental management of general injection workplaces, it was necessary to establish procedures to prevent the environmental management of injection water room and contamination by workers.
– Although the injection water room was located inside the general injection workplace and managed to grade D in cleanliness, the possibility that the injection production worker entering the sterile workshop after high temperature work in the main room could adversely affect the cleanliness of the general injection workshop as there were no other restrictions on maintenance work of the injection water storage could not be ruled out.

○ In order to confirm the adequacy of the HEPA filter installed in the clean booth, it was necessary to indicate and manage the initial differential pressure when replacing.
– The HEPA filter was installed in the clean booth to manage the environment, and the differential pressure gauge was installed to check the normality of HEPA filter. In order to properly carry out the normal range verification procedure, the indication of the differential pressure at the time of initial installation and the differential pressure required to be replaced could not be confirmed.

○ It was necessary to properly control the differential pressure between different areas of cleanliness.

- For the environmental management of clean areas, we managed to maintain the differential pressure between cleanliness, and set the differential pressure standards to conduct regular inspections. Differential pressure between general injection hallway (C205, CNC) and raw material import room (C241, D area) was checked and recorded, but real differential pressure measured was between the hallway (C205) and the inner hallway (C242) was checked. The differential pressure could not be determined for the zone where cleanliness is changed from the CNC zone to the D zone (between hallway and the raw material import room).

○ It was necessary to properly manage the test method for the drop bacteria test and the worker surface bacteria test during environmental monitoring.

- For drop bacillus test, the test was conducted by exposing each of them separately (about 1 hour 30 minutes) during the working hours but conducting the test with continuous exposure of up to 4 hours including lunch time was needed. In the case of worker surface bacteria, only one of the workers was tested, but it was necessary to test the surface bacteria for all possible workers.

  ※ Rules for the Safety of Pharmaceuticals [Appendix 1] 2.3 Environmental Management

  ※ Regulations on Pharmaceutical Manufacturing and Quality Control [Appendix 1] 13. Process Operations

3)	Organization	Personnel (2)/Organization

Key checklist

□ Organization

○ Regulation of division of duties management

- Document number: SOP-21, confirmation date 2019.1.21
- Responsibilities and authorities of the manager of quality department manager, manufacturing department manager, manufacturing process manager, quality assurance manager, manufacturing hygiene manager, quality organization, quality assurance organization, production organization, facility management organization, etc.

○ Communication management regulation

- Document number: SOP-17, confirmation date 2018.2.9.
- The GMP committee's organization and management, GMP organization chart were managed.
- The GMP committee requires monthly meetings and at least one quarterly meeting if there is no agenda.
- 2018 GMP committee minutes were confirmed.

○ Quality department manager and manufacturing department manager division of duties

- Document number: SOP-21A-0001, confirmation date 2017.7.3.
- Dong-A ST had two quality department managers and two manufacturing department managers, operated by nominating them as manager and associate manager. Specific tasks and approval targets were specified and managed by each person in charge.

Deficiency

○ Not Applicable.

4)	Documentation (4)	Documentation (4)

Key checklist

□ Product standard sheet

○ Dong-A Opalmon tablet product standard sheet (document number: DMF-0011, confirmation date: 2019.4.2.)

- Change the name of the excipient (microcrystalline cellulose) ingredient from the drug substance and its quantity to the standard name, and the product standard has been revised to reflect changes in the drug substance and its quantity.
- Storage method: Airtight container, room temperature storage
- Use period: 3 years
- Approved test standards and test methods, preparations in the manufacturing process, manufacturing instructions for packaging workers, and test reports were prepared.
- It has been confirmed that the method of registration of licensed raw materials is identical to that of product standard.

○ Dong-A Perdipine injection (nicardipine hydrochloride) permitted articles confirmation.

- Deleted subsidiary manufacturer (17.12.28)
  - Subsidiary manufacturer (Astellas Tokai, Japan) was registered other than original manufacturer (Daito Pharmaceutical) before change, and it was deleted.
- Packing unit details (18.6.22)
  - Packing unit of 10mLx10 ampules, 2mLx10 ampules were permitted before changes, but packing unit of 10mLx10 ampules that is used when manufacturing was kept and permission of 2mLx10 ampules was deleted.

○ Dong-A Perdipine injection (nicardipine hydrochloride) product standard sheet

- Document number DMF-3025, confirmation date 2019.3.4.
- General Overview, Permission changes and dispositions, Copy of permit, Drug substance and its quantity, Standards and test methods of raw materials, Standards and test methods of materials, Material standard samples, Standards and test methods for semi-finished products, Standards and test methods of the finished product, Quality control facilities and apparatus, Manufacturing process chart, Manufacturing facilities and apparatus, Manufacturing instructions, Packing instructions, Yield Management Standards by Process were managed.
- Manufacture methods: raw material weighing, preparation, filtration, filling, sealing, sterilization, packaging.
- Process inspection: preparation (time, pressure, temperature, pH), filtration (integrity), filling (filling quantity, quantity), sterilization (pressure, temperature, time), sealing (density).

- Material of direct container packaging: brown glass ampule (KP)
- Packaging unit: 10mLx10 ampules
- Manufacturing unit: 420,000mL (40,000AMP)
    - 2017.12.29. manufacturing unit change processed (315,000mL → 420,000mL)
    - Change authorization (management number 20171229, confirmation date 2018.1.19.) and change management report (management number 20171229, confirmation date 2018.6.29.) were confirmed. As the unit of manufacture changes and the ampule and sterilization loading pattern changes, relevant standards are revised, stability tests are carried out, manufacturing instructions and records are changed, facility history cards are changed, packing instructions and records, process validation is performed, cleaning validation is performed, and sterilizer performance qualification is evaluated.
    - In the case of cleaning validation, an impact assessment was conducted by reviewing whether the worst items were changed and the residual allowance criteria after preparing the plan, and the result report was generated.
- Main ingredient: nicardipine hydrochloride (JP)
- Main ingredient manufacturer: Daito Pharmaceutical Co., Ltd.Factory/326, Yokamachi, Yoyama-city, Toyama, 939-8221, Japan (2017.12.28, subsidiary manufacturer Astellas removed)
- 3% of the main ingredient was overdosed based on process validation results.
    - Perdipine hydrochloride main ingredient overage verification report (document number PVR-Q5-PD-021, confirmation date 2013.12.2.) was confirmed and validation was performed for three manufacturing units (1311050, 1311051, 1311052) to confirm appropriateness of 3% overdose of the active ingredient depending on in-process losses.
- Finished product standard and test method: Company standard
    - Appearance, Identification, pH, Purity Test, Insoluble Matter Test, Injectable Use Test, Sterility Test, Content Test
- Storage method: shading, room temperature
- Use period: 2 years from manufactured date
- Raw material storage conditions: based on raw material storage management regulations (SOP-08A-0003).
- Raw material test expiration date: based on the retesting rule of raw material (SOP-09B-0006).
- Yield Management Criteria for Each Process: The yield management criteria for each process were established in accordance with the relevant standards and were drawn up and integrated for all the injections.

□ Gemcit injection (Gemcitabine Hydrochloride) Product Standards

○ Product standard number: DMF-3011

- Packing material: glass vial (KP), rubber cap (KP)
- Manufacturing unit: 10,000V (packaging unit is 1V)
- Following details related to product standards were confirmed.

Check list	Result

Product name, formulation, appearance	Gemcit injection (Gemcitabine Hydrochloride) Injection (freeze-dried injection) This injection is a white powder, contained in a colorless, transparent vial that melts when used.
Efficacy, effectiveness, usage, and capacity, cautions for use	○
Manufacturing process flow chart and detailed manufacturing method by process, process inspection method (if entrusted manufacturing, the range of the entrusted process)	Manufacture process: Raw material weighing → manufacture → filter → Filling and anti-tilting → Freeze drying → Sealing → Packing Process inspection items were set for each process. There was no overdosing of the main ingredient, and no correction was made for the content.
Standard for theoretical output and yield control by process	Filling: 90.25~100.0% Packing: 89.10~100.0% Manufacturing unit: 10,000EA (40,000mL)
Caution during operation	Listed in manufacturing instructions and records
Criteria and testing methods for raw materials, semi-finished products and finished products	- Raw materials: Gemcitabine hydrochloride (USP), D-mannitol (KP), Sodium acetate hydrate (KP), Sodium hydroxide (KP), Hydrochloric acid (KP), injection water (KP), Cap (own standard), Vials (own standard), Rubber cap (own standard), other packaging materials were set and managed by company standards. - Semi-finished product (own standard), completed product (Annex)
Facilities and equipment required for manufacturing and quality control	Facilities and equipment required for manufacturing and quality control confirmed.
Storage conditions	Semi-finished product: 15~25 ℃, humidity below 70% Main ingredient (Gemcitabine Hydrochloride): room temperature (1~30℃) Completed product: sealed container, store at 15~30 ℃
Validity period or expiration date	Semi-finished product: Freeze-drying was set at 1 day of weighing to freeze drying and 6 weeks after capping. Main ingredient (Gemcitabine Hydrochloride): two years from manufactured date Completed product: 36 months from manufactured date
Record management	Revision history is managed by each category. Enforcement: 2013.03.25. (established after separation of company)
Manufacturing instructions and records	Management instructions were divided into manufacturing instructions and records and packing instructions and records.

Deficiency

○ Not applicable

5)	Documentation	Documentation

Key checklist

□ Document creation and management

○ Document Management Regulations (document number: SOP-01, effective date: 2018.4.2.)

- Delete GMP instruction and add document about how to give the certificate on 2017.3., Changed the QA approval, control copy, non-control copy, and invalid training stamp in April of same year, In the document name, the policy is the standard work guide, and there were document revisions such as changing one or two lines horizontally in the center of the text in March 2018.

Deficiency

○ Not applicable

6)	Validation	Validation

Key checklist

□ Process validation

○ Process validation (document number: SOP-13A-0001, effective date: 2018.12.17.)

- Major revisions since the previous inspection included the deletion of retrospective validation, the addition of a measure to change the re-valuation date to review, and the addition of RA items such as the addition of specifications and materials during changes in raw materials, if the material is identical.
- Revalidation is divided into regular and change, and re-validation is required according to the revalidation items through RA when raw material change, packaging material change, process change, machine•facility•equipment change, etc. occurs.

○ Dong-A Opalmon tablet process validation

- After Dong-A Opalmon tablet process validation (document number: PVR-Q5-MT-013), no record of re-validation was found.

○ Dong-A Perdipine injection process validation

- The result report of predictive validation performance on 3 consecutive batches based on the change of manufacturing unit and the change of sterilization equipment loading pattern was confirmed.
- Document number: PVR-Q5-PD-071 (different with PQR document number 21)
- Confirmation date: 2018.6.18.
- Manufactured number: PC1805069, PC1805070, PC1805071
- Manufactured date: 2018.5.18., 2018.5.18., 2018.5.23.
- Manufactured unit: 400,000 Amp (previously 300,000Amp)
- Important Process Variables
  - Before sterilization: filter integrity test
  - Sterilization: vacuum, preheat, sterilization temperature, time, cooling temperature, drying pressure
  - Ampule cleaning: air Pressure, water Pressure
  - Ampule sterilization: sterilization temperature, time

  - Preparation: checking water for Injection (Conductivity, pH)
  - Filtration: nitrogen pressure
  - Filling: filling speed, filling range, nitrogen injection pressure
  - After filling: filter integrity test
  - Product sterilization: vacuum pressure, preheating, sterilization temperature, time, cooling temperature
  - Foreign material inspection: sensitivity, inspection view, light strength, spin
- Critical Process Test Items
  - Manufacture: appearance, pH, specific Gravity, content uniformity, viable cell count, sterility test
  - Filling: appearance, pH, formulation uniformity (mass deviation), identification, content, insoluble matter, insoluble fine particles, purity, endotoxin, aseptic, airtightness, practical amount
- Confirmed that important process variables and test items for each process meet the established criteria.

○ Gemcit injection (Gemcitabine Hydrochloride) process validation plan (PVP-Q5-GC-048, 07, 2015.12.08) and report (PVR-Q5-GC-048, 07, 2016.02.01) were confirmed.

- Due to layout changes and capping machine changes (capping machine P4-1007→P4-1311), three consecutive manufacturing units were revalidated in a predictive manner.
- Manufactured number: 1512008, 1512009, 1601010
- Manufactured unit: 10,000 Vial (1Vx4mL=40,000mL)
- Test Items: manufacture - manufacture-high, medium, low (appearance, pH, content uniformity, bioburden test), filling and anti-tilting-early, mid, late (mass deviation, content, sterility test), freeze drying and sealing-early, mid, late (appearance, pH, insoluble matter, air tightness, mass deviation, identification test, content test, leading material test, endotoxin, sterility test, insoluble particulate test)
- Important process variables
  - Vat, Ring sterilization: air pressure, supply PSG Steam pressure / sterilization process check: maintain 121 ℃, 20 minutes.
  - Instrument and rubber cap, cap sterilization: air pressure, supply PSG Steam pressure / sterilization process check: maintain 121 ℃, 20 minutes.
  - Sterilizer tunnel operation: sterilization temperature 350℃, HEPA filter differential pressure, conveyer belt 150mm/min.
  - Vial wash: 60~200BPM
  - Manufacture water: conductivity, pH
  - Manufacture tank operation: stirring speed, stirring time and pH adjustment
  - Filtration process: filter integrity test (before and after filtration)
  - Filling: filling speed, filling range
  - Freeze drying: freeze drying temperature, time, vacuum degree, rubber completeness inspection
  - Capping: capping speed
  - Vial wash: washing speed
  - Inspection: visual foreign matter inspection, air tightness test

○ Badge filling test (anticancer agent filling line) plans (PVP-Q5-VI-043, 26, 2018.11.21.) and report (PVR-Q5_VI-043, 26, 2018.12.17.) were confirmed.

- Badge filling test was performed regularly every 6 months. Initially, three times were carried out, and three times when there were germ outbreaks or important changes, and regular badge filling tests were required to be conducted only once.
- Target Process: Filtration, filling, anti-tilting, freeze drying, capping
- Badge filling test was carried out 6000 vials, filling 70 mL vials with 35 mL badge (largest vials filled at maximum fill volume).
- 7 workers participated. 7 people were selected as the worst condition than four existing workers. It was conducted in three shifts in the morning, afternoon, and night shifts.
- TSB (Tryptic Soy Broth) was used as filling badge, badge's manufactured concentration was manufactured maximum 212L of 27.8g/L concentration. Non-sterile badge was prepared, sterile filtered and used for filling. Badge performance test was conducted, and bioburden test (right after manufacturing, 3 hours after manufacturing) was performed on the prepared badge.
- Completeness test of sterile filter was conducted before and after use to confirm suitability.
- Environmental monitoring was conducted on floating particles, floating bacteria, drop bacteria, and surface bacteria (worker-forehead, mask, elbow, wrist, finger, equipment surface-before cleaning and before cleaning). The suspended particles were measured from the assembly stage of the parts.
- 380 minutes (6 hours 20 minutes) was charged in consideration of the actual work on the filling time and filling speed, the maximum work time of the process was set to reflect 6 hours, charged 2000 vials with a minimum speed of 13V / min, the maximum speed was 70V / min and charged by 4000 vials. The freeze-drying process was left for 20 minutes.
- During freeze-drying, nitrogen input process was performed by sterilizing filtered air for growth of bacteria.
- Carried out for breakage and fall of container during filling by interference operation, jamming when rubber field is inserted, repair and replacement assuming equipment failure, leave work during lunch break.
- After filling the badge, incubation was conducted at 20~25 ℃ for 7 days and at 30 to 35℃ for 7 days, total incubation for 14 days and observed. Control group testing was performed on the badge.
- A total of 5,811 vials were charged in badge filling test, and no contamination was found.
- List of standard bacteria of Pseudomonas aeruginosa (ATCC6538), Candida albicans (ATCC 10231), Aspergillus niger (ATCC16404), Bacillus spizizenii (ATCC 6633), Clostridium sporogenes (ATCC11437), Salmonella typhimurium (ATCC14028) were possessed, disposable and discarded after test.

□ Major equipment qualification test

○ How to perform facility performance qualification test

- Document number SOP-14B-0003, confirmation date 2018.1.5.
- The types of equipment subject to qualification, re-qualification cycles, and test items for qualification are specified.
- Major facilities and sterilizers in the sterile process are prescribed to be performed once a year.
    - Target equipment: sterilizer, freeze dryer, vial washer, liquid filling machine, capping machine, vial external washer, ampule washing machine, ampule liquid filling machine, ampule inspector, disc inspector, auto foreign material checker, etc.
- It is stipulated that facilities and QC test facilities that operate 24 hours a day should be conducted once a year.
    - Cold room, refrigerator, freezer, room temperature, thermo-hygrostat, constant temperature water tank, dry oven, incubator, etc.
- For other facilities, a risk assessment was conducted to establish a cycle.

○ Dong-A Opalmon tablet major equipment qualification test
- After the previous inspection, the performance qualification of the automatic tester (2) (B020) Tablet Inspecting M/C (P1-0172) was re-evaluated (document number: PQR-Q4-AT-002) and the report was confirmed.
    - Applicable standard: discharge all defective samples
    - Interlock test: Genuine 10,00T, Poor 100T
    - For defective samples, the test was conducted for shortening and interlocking with the test using defective samples such as black tee, white tee, and shredded tablets. All test results are compliant with the application criteria.

○ Ampule washer performance qualification test
- Management number: P4-1269
- Document number: EQR-Q5-WA-052
- Confirmation date: 2019.2.14. (performed yearly)
- Wash rate verification test, Nacl challenge test and final wash solution test (TOC, pH, conductivity) were conducted for minimum and maximum ampule specifications.

○ High pressure steam sterilizer performance qualification test
- Management number: P4-1194
- Document number: PQR-Q5-AC-041
- Confirmation date: 2019.4.25.
- Vacuum leakage test, air removal test (Bowie-dick test), heat distribution test, heat penetration test, microbial killing test
- Heat distribution checked in empty chamber: 121.0±2.0℃, 20 minutes
- Check heat penetration by loading pattern: Fo over 12
- Microbial killing test: BI checked (incubation temperature 60℃, incubation time: 24 hours (48 hours for ampule). * BI: Geobacillus stearothermophilus

○ Dry heat sterilizer performance qualification test
- Management number: P4-1016
- Document number: PQR-Q5-DH-025

- Confirmation date: 2019.5.20. (performed yearly)
- Heat distribution test (setting temperature within 260±15℃), heat penetration test (Fp>30), endotoxin test (3Log reduction)

○ Manufacture tank performance qualification test
- Management number: P4-1041
- Document number: PQR-Q5_SN-085
- Confirmation date: 2017.11.17.
- Rotational speed verification test

○ Ampule rechargeable waste performance qualification test
- Management number: P4-1268
- Document number: PQR-Q5-FL-040
- Confirmation date: 2018.12.10. (performed yearly)
- Verification is done for the minimum and maximum ampule respectively.
- Filling speed test: 130~380 ampule/Min
- Filling amount test: validation within 1% of the minimum and maximum speed respectively.
- Airtightness test and sealing ability test performed

○ Automatic foreign object inspector qualification test
- Newly installed in year of 2018.
- Management number: P4-1397
  (1) Installment qualification test: document number: IQR-P4-AT-064, confirmation date: 2018.7.9.
  (2) Operation qualification test: document number: OQR-P4-AT-065, confirmation date: 2018.7.9.
  (3) Performance qualification test: document number: PQR-Q5-AT-063, confirmation date: 2018.9.27.
- The rotation speed test, the test speed test, the foreign material test, and the test accuracy test were conducted.

○ Gemcit injection major equipment qualification test
- Freeze dryer performance qualification test result report (PQR-Q5-FD-022)
  - Machine management number: P4-1133
  - Performance qualification test was performed in October 2018.
  - Validation items: vacuum leakage test (1x10-2 mbar.L/s), temperature distribution test (set temperature (45℃, 0℃, ±3.0℃)), in-chamber sterilization test(SIP)(121.0℃, maintained for over 30 minutes, Fo value over 15), biological indicator challenge test (BI Test, Geobacillus stearothermophilus, ATCC No.7953)
  - Performance qualification test was performed yearly.
- Tunnel sterilizer performance qualification test result report (PQR-Q5-TU-017)
  - Machine management number: P4-1204
  - Performance qualification test was performed in June 2018.

  - Operation condition: conveyer belt speed: 150mm/min, set temperature: 320±15℃
  - Validation items: wind speed test (Preheating, Cooling Zone 0.5±0.1m/s, sterilization zone: 0.9±0.1m/s), conveyor speed setting test (within ±10mm/min of set value), heat distribution test (within ±15℃ of set value), heat penetration test: FH Value (FH over 30), endotoxin challenge test (3 Log Reduction)
  - Performance qualification test was performed yearly.
- Autoclave steam sterilizer performance qualification test result report (PQR-Q5-AC-035)
  - Machine management number: P4-1132
  - Performance qualification test was performed in May 2018.
  - Operating conditions: verified by setting sterilization cycle (Cytotoxic Cycle, Ring Cycle, Vacuum Leakage Cycle, Bowie Dick Cycle), and operated at over 121.0℃, 20 minutes.
  - Validation items: Vacuum leakage test (at vacuum equilibrium condition, check whether over 12mbar/10min was leaked for 10 minutes), Bowie Dick Test (color change of indicator), heat distribution test (over 121.0℃, 20 minutes maintenance and minimum and maximum deviation of 2.0℃ or less), heat penetration test (F0 value over 12), biological indicator (BI Test, Geobacillus stearothermophilus, ATCC No.7953).
  - Performance qualification test was performed yearly.
- Filling machine qualification test
  - Revalidation performed by resetting operating speed range.
  - Machine management number: P4-1197
  - Performance qualification test was performed in June 2014.
  - Validation items: The minimum and maximum standards according to the specifications of vials (13~100mm/min), specifications of rubber cap, and caps were verified. Check filling rate (within ±5% of set value), filling amount (within 1.2g, 102g±1%), wiring before rubber, oxygen amount.

□ Washing validation

○ General injection AMP aliquot manufacture instrument and filling set washing validation report

- Document number: CVR-Q5-WA-026, confirmation date 2017.5.27.
- In case of aliquot and manufacture instrument, used as only by product, and manifolds and filling sets were shared.
- According to the change of the dispensing mechanism of the filling waste container, the worst item in the ampule formulation was selected as a perdipine injection solution and the cleaning validation was performed.
- Target equipment/facility: scoop, material weighing container, measuring cylinder, beaker, flask, hose, filling set, manifold, preparation tank
- Samples were taken from the 3 manufacturing units (PC1705342, PC1705343, PC1705344) using a swab or rinse method, followed by visual inspection, residual amounts of principal components (HPLC), residues of detergents (TOC, conductivity), pH, microbial testing, and endotoxin testing.
- Used detergent was P3 Cods CIP 90.

- The allowable period before cleaning was verified by 4 ~ 5 hours for each equipment, but it was operated by cleaning immediately after work without applying this in actual manufacturing.

○ General injection facility CHT setup wash validation
- Document number CVR-Q5-SD-016, confirmation date 2017.3.30
- Target equipment/facility: scoop, material weighing container, measuring cylinder, beaker, flask, hose, filling set, manifold, pressurize tank, preparation tank
- The validity of the cleaning time was verified for the equipment with the maximum capacity for each device. Samples were collected 4, 7 and 6 days after the end of washing for each of the three manufacturing units, and microbial sieve (bacteria, fungi) and endotoxin tests were conducted and found to be suitable. Accordingly, the cleaning effective time is set to 4 days and managed.

○ Verification of recovery rate by validation and collection method of testing method for residues of main ingredients and cleaning agent.
- Document number CVR-Q5-PD-008, confirmation date 2015.6.10.
- For the swap method and the rinse method, linearity, limit of detection, limit of quantification, and reproducibility tests were performed to confirm the recovery of the principal components.

○ Anticancer agent aliquot, manufacture instrument and filling set wash validation plan (CVP-Q5-TI-005, 03, 2016.12.23.) and report (CVR-Q5-TI-005, 03, 2017.04.18.) were confirmed.
- Revalidation based on worst case change according to additional item was performed.
- Target equipment: scoop, spatula, material weighing container (SUS), beaker (plastic), measuring cylinder, volume flask, hose (silicon), filling cylinder, nitrogen filling set, nitrogen bubbling set, magnetic bar, margin distributor.
- Washing method for freeze dryer was CIP, SIP, and other equipment and parts were Cop, and detergent was 1% P3-Cosa CIP 90.
- The worst-case items were selected by setting parameter with main ingredient capacity, main ingredient solubility, washing difficulty, toxicity, annual yield, lot total weight, and Meinta injection 100mg (sodium pemetrexed). Subsequent product was selected as 10mg of ADM (doxorubicin hydrochloride).
- The verification items were verified for main ingredients, cleaning agents and microorganisms.
- Tolerance limit was evaluated based on daily limit and general limit value, and the standard was set as 10ppm which is general limit value.
- Main ingredient, cleaning agents sample collection was performed by using rinse method, microorganisms sample collection was performed by using swab method.
- DHT: wash the day of, CHT: set as 10 days.
- The main component was validated by HPLC test method and tested for cleaning agent (TOC).
- Validation document (CVR-Q5-SD-016) of injection CHT setting was confirmed, performing verification for 3 times and set as 10 days (verification of re-washing was performed).
- Test method validation verification parameter was performed as detection limit, quantitative limit, linearity, precision, accuracy, set as over 70% for recovery rate, and verification performed SUS, which is verification material.

○ Freeze dryer wash validation plan (CVP-Q5-GC-041), 05, 2014.12.08.) and report (CVR-Q5-TI-005, 03, 2017.04.18) were confirmed.

- Terarubicin injection 20mg (Pirarubicin) was selected as worst product.
- Validation target: freeze dryer, Ring
- Wash method: CIP, SIP
- Visual inspection, principal component, microorganism, endotoxin and antidote were verified for verification target, and no poison or cleaning agent was used in the freeze dryer.
- Freeze dryer and Ring were used as common equipment.
- Verification for CHT was not performed because it was rewashed before use.
- Material swab and rinse methods were used for sample collection method, detergent, endotoxin, antidote used rinse method, and microorganism used swab method.
- Recovery rate verification (SUS) and test method validation were performed for major ingredient, verification for linearity, detection limit, quantitative limit, reproducibility validation was performed for verification parameter, performing swab method and rinse method separately.
- Compliant with the verification result criteria.

□ Manufacturing support facility validation

○ Air conditioner validation

- Document number EQR-Q5-AH-185, confirmation date 2019.1.9.
- Performance qualification test was completed for AHU#1 in 2015 (phase 1 (PQR-U1-AH-149, 2015.01.12), phase 2 (PQR-U1-AH-149, 2015.06.30.), phase 3 (PQR-U1-AH-149, 2015.12.29.) and requalification test of the air conditioner was conducted twice a year regularly.
- After confirming the calibration condition of the test equipment, it was found suitable by conducting tests on temperature, humidity, floating bacteria, floating particles, drop bacteria, surface bacteria, ventilation frequency, differential pressure, etc.

○ Compressed air, nitrogen gas manufacture and distribution system performance qualification test

- First half of 2018 compressed air quality test document were confirmed.
  - Document number PQR-Q5-OF-014, confirmation date 2018.7.31.
  - Floating particle content, dew point (humidity), oil content, and microbiological tests (floating bacteria) were conducted at the compressed air and nitrogen gas supply facilities and the point of use.
  - Requalification test was conducted every 6 months, the filter replacement cycle at the point of use.

○ Manufacture water validation

- Distilled water system 1Loop performance qualification test report
  - Document number PQR-Q3-PW-028
  - Requalification test was conducted based on 1Loop system change occurring, some warning level deviation occurred but no action level deviation was evaluated as appropriate.

- Phase I: performed for 10 days in a row, every day, 2018.4.26. ~5.5.
- Phase II: performed for 2 weeks, every day, 2018.5.4. ~5.23.
- Phase III: performed for 11 months, once a month, 2018.5.18~2019.4.24.
- Test items: Form (KP), pH (self), Conductivity (USP at 25℃ standard), TOC (USP), General Bacteria (USP)

– Injection water system performance qualification test report
  - Document number PQR-Q5-WI-064
  - Requalification test was carried out according to the establishment of new point of use (Trial Filtration Room, INJ-64), and evaluated as appropriate since no deviation occurred.
  - Phase I: performed for 10 days in a row, every day, 2018.4.24. ~5.8.
  - Phase II: performed for 10 days, every day, 2018.5.8. ~5.23.
  - Phase III: performed for 11 months, once a month, 2018.5.24~2019.4.24.

○ Anticancer agent building air conditioner (AHU-101) performance qualification test
– Purpose: air conditioner re-validation was performed based on layout change in air conditioner (AHU-101) area.
– The risk assessment (air conditioning system risk assessment method) was conducted for some areas (wall movement) of the manufacturing workshop, and only phase I was changed due to minor changes.
– Phase I was performed for 1 day for area of air conditioner (AHU-101).
– Enforcement period: Phase I: 2018.05.14.(1 day)
– Area: aseptic undressing front room (C306)
– Evaluation items: Preparation, review, approval of protocol, environmental monitoring (floating particles, floating bacteria, drop bacteria, surface bacteria), temperature and humidity check, differential pressure check.
– For air conditioners, the performance inspection items were regularly checked twice a year for the air volume, the frequency of ventilation, and the actual differential pressure.

□ Test method validation

○ Gemcit injection (completed product) standard and test method: separate regulation
– Validation target: identification test, content test, leading material, sterility test, endotoxin test
– Identification test test method validation plan for Gemcit injection 200mg, 1g (MVP-Q2-GC-020, 01, 2009.11.30.) and result report (MVR-Q2-GC-020, 01, 2009.12.07.)
– Test method: TLC
– Verification parameter: specificity
– Content test test method validation plan for Gemcit injection 200mg, 1g (MVP-Q2-GC-033, 02, 2012.02.06.) and result report (MVR-Q2-GC-033, 01, 2012.02.16.)
– Test method: HPLC
– Verification parameter: System suitability, precision (repeatability, laboratory precision), straightness and range, accuracy, specificity, robustness (flow rate-1.0mL/min/1.4mL/min, temperature -27℃/33℃, safety-24 hours)
– Verification was performed at a range of 80 ~ 120% of standard solution.

○ Lead material test test method validation plan for Gemcit injection 200mg, 1g (MVP-Q2-Gc-24, 01, 2010.03.29.) and result report (MVR-Q2-GC-024, 01, 2012.03.29.)

- Test method: HPLC
- Verification parameter: System suitability, precision (repeatability, laboratory precision), linearity and range, accuracy, specificity, limit of quantitation, limit of detection, robustness (flow-1.0mL/min/1.4mL/min, temperature-27℃/33℃, safety-24 hours)

□ Machines and instruments used for test qualification test

○ GC(Q2-6116) performance qualification test report (EQR-Q2-GC-062)

- Qualification test was performed due to new equipment introduction.
- Test schedule: 2019.01.30
- Verification items: system inspection and basic safety and operation, GC oven temperature accuracy and stability, inlet pressure decay, inlet pressure accuracy, detector flow accuracy, signal noise and drift, signal to noise.
- Performed by manufacturer Agilent Technologies.

○ U-3000 HPLC(Q2-6105) performance qualification test report (EQR-Q2-LC-301)

- Qualification test was performed due to new equipment introduction.
- Test schedule: 2018.09.12
- Verification items: injection and Flow Precision, Pump Gradient 1, 2, 3, Pump Gradient Precision, Injection Carry Over, Injection Linearity, Injection Temperature Accuracy, Temperature Accuracy Column Oven, UV detector Noise and Drift, Wavelength Accuracy DAD Detector, UV Detector Linearity confirmed.
- Performed by manufacturer ThermoFisher.

○ Autoclave steam sterilizer (Q2-7009) performance qualification test result report (PQR-Q5-AC-044)

- Test schedule: 2019.02.20. ~2019.02.28.
- Test items: vacuum leak test, heat distribution test, heat penetration test (Fo value over 12.0), biological indicator test, Bowie Dick test
- Sterilization temperature (121.5℃), sterilization time (20 minutes)
- Loading pattern: classified as 3 cycle, aseptic clothes, filter, badge.
- Performed by own company.

○ Absorbance Microplate Reader performance qualification test result report (EQR-Q2-MR-020)

- Test schedule: 2018.06.21.
- Verification items: Password Security Test, Password Timeout Test, Command Output Test, Interrupted Communication Test, Abort Function Test, Kinetic Noise Test, Temperature Uniformity Test, Universal Plate Test, Universal Plate Test Reversed.
- Performed by Charles river.

○ Dissolution tester (Q4-9044 & Q4-9047) performance qualification test result report (PQR-Q5-DN-069)
- Test schedule: 2019.03.19.
- Verification items: location, number and color verification of Vessel and Shift, vessel temperature, Vertical Tester moving at a center, Wobble, RPM, Apparatus Suitability Test, Performance Confirming, Sampling Accuracy.
- Performed by own company.

Deficiency

○ Not applicable

7)	Quality Control	Quality Control

Key checklist

□ Test report

○ Dong-A Opalmon tablet test record (completed)
- Manufactured number: OMT11706003, OMT1812120, OMT1901121
- Test standard: own
- Test items: appearance, identification, content, disintegration, leading material, formulation uniformity (content uniformity, mass deviation), hardness, wearability, packing inspection
- All test items met the test standard and there were no specifics such as deviation.

○ Dong-A Opalmon tablet main ingredient test record
- Management number: 181200021
- Test standard: JP
- Test items: appearance, identification, non-linear luminance, leading material, moisture, quantification
- All test items met the test standard and there were no specifics such as deviation.

○ Primary material test record (AL-FOIL275-B)
- Management number: 190100017
- Test standard: own
- Test items: appearance condition, color, packing, wrapping condition, pin hole, specification, fluorescent material, elution, residue
- All test items met the test standard and there were no specifics such as deviation.

○ Dong-A perdipine injection solution shipping approval form
- The quality department manager make final approval of the shipment by reviewing the manufacturing and packaging instructions, the finished and semi-finished test records, change control items, deviations and standard deviations, manufacturing water and environmental monitoring.

○ Dong-A perdipine injection solution completed product test report
- Manufactured number: PC1801044 (manufactured date 2018.1.11.)
- Appearance, identification test, pH, practical amount, insoluble matter, content test, purity test, sterility test, endotoxin, insoluble fine particles, packaging test (density, case, insert, label, ampoule sealing state, etc.)

○ Main ingredient (nicardipine hydrochloride) test report
- Test specification: JP
- Manufactured number (test number): 17001Y1 (CPU00000925)
- Test items: appearance, identification test (UV, IR chloride), melting point test, heavy metals, leading materials, loss on drying, residual burn, quantitative test, endotoxin

○ Ampule (primary material) test report
- Test specification: KP
- Manufactured number (test number): A1711-510 (CPU00002317)
- Test items: appearance condition, color, cleanliness, point check, cutting, size measurement, strain, alkali dissolution, colored container iron dissolution, light shield test.

○ Gemcit injection completed product QA record
- Manufactured number: GC1803003, GC1808004, GC18011005
- Manufactured date (suitable date): 2018.03.13. (2018.04.09.), 2018.08.14 (2018.10.02.), 2018.11.28. (2018.12.20.)
- Test standard: separate standard
- Test items: appearance, identification test (TLC, HPLC), pH, formulation uniformity test (mass deviation), insoluble matter, airtightness test, leading material (cytosine, a-anomer, other individual leading materials, total leading material), content test, aseptic test, endotoxin test, insoluble fine particles, packaging inspection
- Confirmed that the badge performance test was performed for sterility test.
    - TSB: verification was performed on *Bacillus Spizizenii* (ATCC 6633), *Candida albicans* (ATCC 10231), *Aspergillus niger* (ATCC 16404), incubating for 5 days at 20~25℃, and result was suitable.
    - FTM: verification was performed on *Staphylococcus aureus* (ATCC6538), *Pseudomonas aeruginosa* (ATCC9027), *Clostrium sporogenes* (ATCC11437), incubating for 5 days at 30~35℃, and result was suitable.

○ Gemcit injection (Gemcithavin hydrochloride) ingredient and material QA record
- Gemcithavin hydrochloride (main ingredient) report
    - Test number (manufactured date): CPU00005861 (2018.08.18), CPU00004185 (2018.05.10), CPU00003325 (2018.02.21)

  - Test standard: USP
  - Test items: appearance, identification test (FT-IR, reagent reaction), non-linear luminance, pH, leading substance (Cytosine Gemcitabine a-anomer, other individual leading substances, total leading substances), ignition residue, quantification, residual solvent (methanol, acetone, dichloromethane, tetrahydro hulan, ethyl alcohol, Anisole), endotoxin
  - Manufacturer: Kyeongbo pharmaceuticals, 174 Sil-ok ro, Asan-si, Chungcheongnam-do
- Deviations occurred in reconfirming the results due to missing some peaks in the lead material test (190529-01), recalculation of the results confirmed the suitability, and training for workers took place.
- Hydrochloric acid (excipient) report
  - Test number (manufactured date): R6070092 (2015.11.20.)
  - Test standard: KP
  - Test items: appearance, weight, identification test (solution reaction, qualitative reaction of chloride), purity test (sulphate, sulfite, bromide or iodide, bromine or chlorine, heavy metals, arsenic, mercury), ignition residue, quantification
  - Manufacturer: Merck KGaA, Frankfurter Straβe 250, 64923 Darmstadt, Germany
- Sodium hydroxide (excipient) report
  - Test number (manufactured date): CPU00001296 (2016.09.01.)
  - Test standard: KP
  - Test items: appearance, identification test (solution reaction, qualitative reaction of sodium salt), dissolved state, chloride, heavy metal, potassium, sodium carbonate, mercury, lead, arsenic, quantification, endotoxin
  - Manufacturer: Merck KGaA,
- D-mannitol (excipient) report
  - Test number (manufactured date): R7030042 (2016.05.31.), CPU00000217 (2016.06.09.)
  - Test standard: KP
  - Test items: appearance, identification test (precipitation reaction, FR-IR), non-linear luminance, melting point, purity test (dissolved state, acid, chloride, sulfate, heavy metals, nickel, arsenic, sugars, glucose), loss of drying, conductivity, ignition residue, leading substance (sum of D-sorbitol, maltitol & isomalt, other leading substance, total leading substance), quantitative test, endotoxin, microbial limit test (total aerobic microbial count, total fungal count), identification test by container.
  - Manufacturer: ROQUETTE FRERES, 1 RUE DE LA HAUTE LOGE, 62136, LESTREM FRANCE
- Sodium acetate hydrate (excipient) report
  - Test number (manufactured date): R7010079 (2015.06.05.)
  - Test standard: KP
  - Test items: appearance, identification test (acetic acid salt reaction, sodium salt reaction), purity test (dissolved state, acid, alkali, chloride, sulfate, heavy metal, calcium and magnesium, mercury, lead, arsenic, potassium permanganate reducing substance), drying loss, quantification, endotoxin

- Manufacturer: SIGMA-ALDRICH, 3050 Spruce Street Saint Louis MO 63103, USA

– ADM10 Vial (primary packing material) report
  - Test number (manufactured date): CPU00004956 (2018.06.28.), CPU00005672 (2018.08.08.)
  - Test standard: KP (own standard)
  - Test items: appearance condition, color, cleanliness, vial top smoothness, capping & sealing, size measurement (inner diameter min. & max., height min. & max., bottle outer diameter min. & max., bottle height min. & max., outer diameter min. & max., thickness min. & max., weight (mass) min. & max., capacity min. & max., strain, alkali elution, arsenic, hydrolysis resistance
  - Manufacturer: Shinil Pharm Glass Co., LTD

– Rubber cap (primary packing material) report
  - Test number (manufactured date): CPU00006111(2018.07.19.), CPU00006373 (2018.07.19.), CPU00006504 (2018.11.02.), CPU00005315 (2018.07.19.)
  - Test standard: KP (own standard)
  - Test items: appearance condition, color, cleanliness, capping & sealing, size measurement (external diameter min. & max., bend external diameter min. & max., thickness min. & max., inner thichkess min. & max., height min. & max., weight (mass) min. & max., quality of material (Butyl), lead, cadmium, eluate from sap rubber stopper test (transmittance, foam, pH, zinc, reducing potassium permanganate, evaporation residue, UV absorbance), endotoxin
  - Manufacturer: Yungjin Industrial Corporation
  - Separate samples were supplied from the manufacturer.

– CAP (primary packing material) report
  - Test number (manufactured date): CPU00005214 (2018.07.18.), CPU00006112 (2018.09.19.), CPU00006445(2018.10.25.)
  - Test standard: own standard
  - Test items: appearance condition, type, pp material color, aluminum color, size measurement (inner diameter min. & max., height min. & max., thichkess min. & max., external diameter min. & max., height min. & max., aluminum hole inner diameter min. & max.,)
  - Manufacturer: Yungjin Industrial Corporation
  - Separate samples were supplied from the manufacturer.

□ Product quality evaluation

○ Regular quality evaluation (SOP-18A-0001, 1, 2019.01.02.)
– Regular quality assessments should be carried out and documented annually, preparing a regular quality evaluation plan, and regular quality evaluation report should be written according to the schedule.

- The types of trend analysis available for product quality evaluation were defined as trend analysis of raw material test results, trend analysis of semi-finished product and finished product test results, manufacturing environment trend analysis, manufacturing water trend analysis, yield trend analysis by process, and others.
- Regulated to include results of product quality evaluation, deviations from standard and deviations during manufacturing and testing, change control related to manufacturing control and quality control, process validation results, stability results, customer complaints and recalls, processing results for returned products (returns), supporting facility qualification evaluation, post marketing, contractual agreements, details of nonconforming products (only for the export of anticancer agents injection), and the results of corrective actions.
- Addition of corrective measures for trends and abnormalities.

○ 2018 Dong-A Opalmon tablet product quality evaluation (document number: APR-Q3-MT-019)

- Evaluation period: 2018. January ~ December
- Subject of evaluation: Dong-A Opalmon tablet (OMT1712035 ~ OMT1810104, 70 Lot)
- Product quality evaluation: confirmed that the raw material, active ingredient content distribution is managed smoothly.
- It was collected (returned) due to the expiration date and received a request for disposal.
- Raw materials, manufacturing water, manufacturing environment, and product quality evaluations were managed within the standards, and there were no deviations and standard deviations.
- One change management (change management number: 20180516-1) occurred due to the change of the name of the raw material manufacturer and a change approval letter and a change completion report were prepared according to the change management (document number: SOP-20A-001).
- Post-marketing stability test was carried out according to plan and all test items met test standard.
    - Manufactured number (test cycle): 1509135 (36months difference), 1606182 (24 months difference), OMT1708017 (12 months difference), OMT1810097(0-month difference)
    - Test cycle: 0, 12, 24, 36 months
    - Storage requirements: 25±2℃, 60±5%
    - Test items: appearance, confirmation, disintegration, purity (leading substance), formulation uniformity (content uniformity), content, formulation uniformity (formulation uniformity)
    - All test items met the test standard and there were no specifics such as deviation.

○ 2017 Dong-A Opalmon tablet product quality evaluation (document number: APR-Q3-MT-019)

- Evaluation period: 2017. January ~ December
- Subject of evaluation: Dong-A Opalmon tablet (1612203 ~ OMT1711034, 54 Lot)
- Raw materials, manufacturing water, manufacturing environment, and product quality evaluations were managed within the standards, and there were no deviations and standard deviations.

- One complaint (document number: 36214) has been received regarding a tablet breakdown due to packaging failure. Improvement of film transfer guide and improvement of overload sensor
- There was no change management, and the post-marketing stability test was carried out according to the plan, and all the test items met the standard.
    - Manufactured number (test cycle): 1409081 (36 months difference), 1509135 (24 months difference), OMT1708017 (0-month difference)
    - Test cycle: 0, 12, 24, 36 months
    - Storage requirements: 25±2℃, 60±5%
    - Test items: appearance, confirmation, disintegration, purity (leading substance), formulation uniformity (content uniformity), content, formulation uniformity (formulation uniformity)
    - All test items met the test standard and there were no specifics such as deviation.

○ 2016 Dong-A Opalmon tablet product quality evaluation (document number: APR-Q3-MT-019)

- Evaluation period: 2016. January ~ December
- Subject of evaluation: Dong-A Opalmon tablet (1511149 ~ 1610202, 54 Lot)
- Raw materials, manufacturing water, manufacturing environment, and product quality evaluations were managed within the standards, and there were no deviations and standard deviations.
- There were no customer complaints, and there were two cases of change management related to purity, formulation uniformity, content test method change, and detailed description of packing unit, and proceed according to the change management regulations.

○ 2018 Dong-A Perdipine injection solution product quality evaluation

- Document (management) number: APR-Q3-PD-024, confirmation date: 2019.2.12.
- Evaluation period: 2018.1.1. ~ 12.31.
- Manufacturing performance: 80 Lot
- Evaluation was conducted, including In-process test results, raw material results, product test results, manufacturing environment (temperature and humidity, cleanliness), manufacturing water, process yield, deviation and standard deviation, change control, PV, stability test results, customer complaints and recalls, recalled products, correction, measures and details of nonconformities.
- Cpk and Cp values were calculated for process capability and judged to be suitable when Cp was above 1.0 (Cp-0.5=Cpk).
- Post-marketing stability test: 1608276 (16.8.11.), PC1709017 (17.9.4.)

○ Gemcit injection product quality evaluation document

- Evaluation period: April 2016 ~ March 2017
- Document number: APR-Q3-GC-051, confirmation date: 2017.04.24.
- Total of 2 lot (1604011, 1607012) of Gemcit injection was manufactured, raw material quality evaluation, manufacturing water quality evaluation, manufacturing environment management, product process quality evaluation, deviation, result of deviation from standard and reprocessing, all changes related to manufacturing and quality, process validation, stability test (long-term stability, post-market stability), customer complaints and recalls, recovery and return, support facility eligibility evaluation, and corrective action were all evaluated and all met the established criteria.
- A total of one change management (20170117-1) occurred in relation to Gemcit injection products, and a new registration of material (rubber cap) occurred in relation to manufacturing control and quality control.

○ Gemcit injection 2017 product quality evaluation document
- Evaluation period: April 2017 ~ March 2018
- Document number: APR-Q3-GC-051, confirmation date: 2018.05.08.
- Total of 3 lot (GC1707001, GC1711002, GC1803003) of Gemcit injection were manufactured, evaluating in same items as year 2016, and all met the established criteria.
- A total of two change management (20170706-1, 20171110-1) occurred in relation to Gemcit injection products, and gemcitabine injection's temporary manufacturing unit change (10,000V→9,964V) and preparation line capacity change (100L→200L) were confirmed.

○ Gemcit injection 2018 product quality evaluation document
- Evaluation period: April 2018 ~ March 2019
- Document number: APR-Q3-GC-051, confirmation date: 2019.04.29.
- Total of 3 lot (GC1808004, GC1811005, GC1902006) of Gemcit injection were manufactured, evaluating in same items as year 2016, and all met the established criteria.
- A total of two change management (20180531, 20180927) occurred in relation to Gemcit injection products, confirmed that the standard and test method of gemcitabine hydrochloride raw material were changed according to the change of vial material and two revisions of USP41.

□ Safety test

○ Safety test management standards (SOP-09A-001, 10, 2018.09.14.)
- According to the type of stability test, it was classified as long-term preservation test, accelerated test, harsh test, intermediate condition test, and ongoing stability test.
- The manufacturing number subject to the long-term preservation test is to be performed for the first 3 commercial manufacturing units. The test cycle was required to be tested every three months for the first year, every six months for two years thereafter, and once a year after two years, based on the date of request for testing of the finished product (start of test).
- In principle, all items are tested for long-term preservation tests, and, according to the characteristics of the test, the test item could be omitted if there is a special reason such that the change over time is not recognized.
- The test conditions of the long-term preservation test were classified into room temperature storage, refrigerated storage, and frozen storage, and each test condition was specified.
- Post-marketing stability test is conducted from January to December of the current year as of the packing date and the test cycle is conducted for stability test over 3 time points including initial until the expiration date. In the case of more than 24 months, it is carried out every year (0, 12, 24, 36 months), and in the case of less than 24 months, it is stated that the starting point, the intermediate test of the validity period, and 3 time points of the validity period are conducted.

- Post-marketing stability test is regulated to be conducted from January to December of the current year as of the packing date.

  ※ Based on the stability test items reviewed in the data submitted for the drug product renewal application (yearly product quality evaluation), 8 items including Co-Apurtan tablet 300 / 12.5mg and Dong-A Nicetile tablet did not perform post-marketing stability test.

  - Dong-A Nicetile tablet, Varosartan tablet 80 mg, Co-varosartan tablet 80/12.5mg did not perform post-marketing stability test after 2016, Co-Apurtan tablet 300/12.5mg, Apurtan tablet 150mg, Co-varosartan tablet 80/12.5mg, Apurtan tablet 300mg did not perform post-marketing stability test after 2017, Olsartan tablet 20mg, Dong-A Perdipine Long Acting SR capsule 40mg did not perform post-marketing stability test after 2018.

○ Post-marketing stability test (Dong-A Opalmon tablet)

- Document number: STP-Q3-MT-024, (Plan)
- Temperature and humidity: 25±2℃, 60±5%
- Test cycle: initial, 12, 24, 36 months
- Manufactured number: OMT1810097
- Test items: appearance, identification, content, disintegration, purity, formulation uniformity
- Only initial test was completed, when all the tests were completed according to the test cycle, a result report was prepared.

○ Dong-A Perdipine injection solution stability test

- Long-term storage stability test
  - In accordance with the increase in manufacturing units in 2018, a stability test plan was prepared. Although it was replaced with the stability test after marketing in 2018, it was not possible to confirm the test result in progress up to the inspection date.
- Post-marketing stability test
  - Report document number: STR-Q3-PD-028, 2018.10.17.
  - Stability test was performed on 1 manufacture unit manufactured in 2016.
  - Manufactured number: 1608276, manufactured date: 2016.8.11.
  - Test cycle: 0 month, 12 months, 24 months
  - Storage requirement: temperature: 25±2 ℃, relative humidity 60±5%
  - Stability sample amount: 11 Case (*10 ampule)
  - Test items: appearance, identification test, pH, purity test, insoluble matter, practical amount, aseptic test, content test, endotoxin, insoluble fine particles
    - Intermediate test omitted: Identification test, insoluble foreign material test, insoluble particulate test, endotoxin, and sterility test were omitted during the intermediate test because there is no fear of change over time.

○ Gemcir injection 2017 post-marketing stability test plan (STP-Q3-GC-056, 02, 2017.07.25.)

- Type of stability test: post-marketing stability test (25±2 ℃, RH 60±5%)
- Manufactured number and manufactured date: GC1707001 (2017.07.12.)
- Packaging container: vial
- Sample amount: 106V
- Test period: 36 months
- Test cycle: initial, 12 months, 24 months, 36 months
- Test items: appearance, identification test (TLC, HPLC), content, pH, leading substance (cytosine, a-anomer, other leading substances, total leading substance), mass deviation, endotoxin, insoluble matter, sterility test, insoluble fine particles
- Mass deviation, sterility test, endotoxin test, insoluble fine particles test, insoluble matter test are regulated to perform only initial and 36 months.

○ Gemcit injection 2018 post-marketing stability test plan (STP-Q3-GC-056, 04, 2018.09.10.)

- Type of stability test: post-marketing stability test (25±2 ℃, RH 60±5%)
- Manufactured number and manufactured date: GC1808004 (2018.08.14.)
- Packaging container: vial
- Sample amount: 106V
- Test period: 36 months
- Test cycle: initial, 12 months, 24 months, 36 months
- Test items: appearance, identification test (TLC, HPLC), content, pH, leading substance (cytosine, a-anomer, other leading substances, total leading substance), mass deviation, endotoxin, insoluble matter, sterility test, insoluble fine particles
- Identification test, mass deviation, sterility test, endotoxin test, insoluble fine particles test, insoluble matter test are regulated to perform only initial and 36 months.
- Current test cycle has not arrived

□ Archive sample management and records

○ Raw material sample storage management method (SOP-02C-0002, 07, 2019.01.17.)

- The details of the designation of the manager of the sample storage, classifying the accesses to the storage warehouse and management ledger.
- It is stated to be managed for 24 hours based on the temperature and humidity management regulation.

○ Product storage sample, reference sample management method (SOP-09B-2009, 06, 2017.08.16.)

- Separate place is arranged with a lock system to be maintained and managed as storing at a room temperature of 15~25℃, storing in fridge at 2~8℃, cold dark storage at 1~15℃.

- Stated as completed product being stored for 1 year after expiration date (zydena was stored for 2 years after expiration date), clinical products that does not have expiration date being stored for 5 years (extend 2 years of storing period if on-going product).

○ Sample management standards (SOP-09B-2001, 06, 2019.05.08.)
- Sample was collected by the QA team's sampling officer, and sampling was prescribed by adding up the amount necessary for the test and the amount used for later stored sample.
- Raw material storage sample should be stored in storage containers, the storage period of the main ingredient is set to the expiration date of the raw material + the expiration date of the product + 1 year, and the storage product of other components is required to be stored for 5 years.
- Samples for storage of finished products shall be stored in the same form as commercially available products, and it is required to keep it for one year from expiration date.

○ Sample collection amount and storage amount (semi-finished product, completed product) (SOP-09B-2003, 04, 2018.09.10.)
- Storage period of storage product of completed product was regulated as use period + 1 year.
- It was required to keep the test quantity of more than 2 times of all items except sterility test and pyrogenic test.

○ Anticancer agent raw material sample collection method (SOP-09B-2015, 010, 2019.01.22.)
- Package unit quantity to collect main ingredient sample was performed based on WHO guideline n Plan.
- The details of the confirmation and precautions when collecting samples, the methods and precautions for access to the anticancer raw materials sample collection room, and the methods for collecting anticancer drugs were specified. Sample collection tools use disposable instruments, and when collecting anticancer agent raw material, it was required to collect them using a glove box.

○ Packing material sample collection method and quantity (SOP-09B-2006, 004, 2017.08.17.)
- Rubber caps and injection aluminum caps are warehoused after being washed and packed in dust-free bags, so it is required that the vendor receives a separate sample for packaging.
- Sample collection amount was decided (AQL selection) based on ISO 2859-1.

□ Deviation/standard deviation etc.

○ Deviation management regulation (SOP-11A-0001, 12, 2019.04.01.)
- Deviation procedure: deviation occurs → submission to QA → deviation level check → related department meeting (if needed) → cause identification (within 3 days of submission) → establishment of measures → take measures → corrective and preventive action → improvement confirmation verification (If the verification fails to confirm the improvement, recheck the cause) → completion report (within 30 days of submission) → CAPA (if needed)
- Deviation rating was set as Critical, Major, Minor, Error.
- No change after previous inspection.

○ Standard deviation management regulation (SOP-11B-0001, 09, 2017.05.22.)

- Standard deviation work process: OOS occurrence confirmation (tester) → report to QA head → write standard deviation report → submission to QA → nonconformity test → (Before the test result is confirmed) termination of test, log recording, and termination after retest, (after confirming test result) fill out preliminary laboratory investigation → test method • system suitability • tester assessment → sample • test environment survey → if a suspected cause is found, correct the cause and retest (1 time), if no cause is found, perform full laboratory investigation.
- When OOS occurs, preliminary laboratory investigation and full laboratory investigation is performed and managed by processing procedure.
- OOS processing procedure was divided and classified as after preliminary laboratory investigation, if no cause if found, then full laboratory investigation.

Deficiency

<Other>

□ Complement the following with regard to test management:

○ Regarding the form of storage sample packaging for raw materials (primary ingredients), documentation should be available to ensure that the packaging is of equivalent quality, or that the packaging should be the same.

- Dong-A Opalmon tablet's main ingredient, stored in freezer, has final packaging form of glass bottle, the reference sample container in storage is PE, and the sample storage container material could not be confirmed to be equivalent to the final packing material.

  ※ Rules for the Safety of Pharmaceuticals [Appendix 1] 7.1 Test Management

<Important>

☐ Complement the following regarding stability test:

○ After each year, at least one manufacturing unit for each content and type of packaging of the same material as the commercially available product shall be subjected to the post-marketing stability test. In addition, make sure that the product quality is maintained during the use period or the expiration date for 8 items including Co-Apurtan tablet 300/12.5mg that have not been subjected to post-marketing stability tests and come up with measures to prevent recurrence.

- Based on own company standard document 'stability test management standard (document number: SOP-09A-0001)', post-marketing stability tests should be conducted from January to December of the relevant year as of the packaging date, but 8 items including Co-Aprutan tablet 300/12.5mg, and Dong-A Nicetile tablet were manufactured (packaged) and not tested for post-marketing stability.
  - Dong-A Nicetile tablet, Varosartan tablet 80mg, Co-varosartan tablet 80/12.5mg did not perform post-marketing stability test in 2016, Co-Apurtan tablet 300/12.5mg, Apurtan tablet 150mg, Co-varosartan tablet 80/12.5mg, Apurtan tablet 300mg did not perform post-marketing stability test in 2017, Olsartan tablet 20mg, Dong-A Perdipine Long Acting SR capsule 40mg did not perform post-marketing stability test in 2018.

※ Rules for the Safety of Pharmaceuticals [Appendix 1] 7.2 Stability Test

8)	Production management	Production

Key checklist

□ Manufacturing and packing process management

○ Dong-A Opalmon tablet manufacturing order record

- Manufactured number: OMT1706003, OMT1812120, OMT1901121
- Manufactured date: manufacturing order date
- Manufacturing unit: 1,600,000 EA
- Manufacturing process (process test): Freeze drying, drying (LOD) → premix → mix → tableting (disintegration, wear and tear, thickness, hardness, mass deviation) → selection → packing (Compression status, labeling, airtightness status, presence of contents, etc.)
- All processes were produced without deviation without specificity.

○ Dong-A Perdipine injection solution manufacturing order and record

- Manufactured number: 1801043, 1801044, 1801045
- Manufactured date: 2018.1.10., 2018.1.11., 2018.1.11.
- Manufactured process: raw material weighing → manufacturing → filter → sealing → sterilization → sealing test → foreign material test → packing
- During the work, the environmental monitoring results were included and managed.
  - Floating particles, drop bacteria, floating bacteria, surface bacteria: manufacturing room, filling room
  - Worker surface bacteria: filling Room
- Yield management criteria: filling (89.11~100%), final (86.7~100%)
- Before the operation, the cleaning status of the work room and equipment was checked and recorded, and checked the differential pressure, temperature and humidity, and illuminance in the work room.
- Pre-operational test filtration and filter integrity tests were conducted.
- Prior to sterilization process, CI was used to confirm the adequacy of sterilization.
- When importing raw materials, the outer packaging was imported after disinfection.
- pH and conductivity tests were conducted on the injection water used for each operation.
- The injection water was weighed and injected into the manufacturing process after weighing the tank using P4-1342 balance.
- Critical process check
  - Filling tool sterilization: autoclave steam sterilizer (P4-1194), clean booth (P4-1089), sterilization temperature over 121℃, sterilization time 20 minutes

- Ampule washing and sterilization: ampule washing machine (P4-1269), dry heat sterilizer (P4-1016), sterilization temperature 260℃, sterilization time 40 minutes.
- Weighing: daily check was performed on scale (P4-1046) before weighing, weighing in clean booth in manufacturing room, after being weighed with RWS (Raw material Weighing System), weighing chart was printed and attached.
- Manufacturing: daily check was performed on scale (P-1046) before weighing.
- Primary manufacturing: 0.2N-HCL dissolution (180rpm, over 5 minutes)
- Secondary manufacturing: main ingredient dissolution (180rpm, over 10 minutes) and sub ingredient dissolution (180rpm, over 10 minutes)
- pH correction: addition of injection water (180rpm, over 10 minutes) and pH correction (3.3~3.5)
- filtering: N2 pressure filtration by connecting the disinfection filter (0.2㎛) to the manufacturing tank and performing the filter integrity test after filling.
- Filling: as a process inspection of filling waste (P4-1268), filling rate (120~300 Amp/min), target filling amount (10.5mL x specific gravity), the filling amount was measured every 30 minutes and a recording sheet was attached.
- Sterilization: sterilization temperature over 121℃, sterilization time 20 minutes
- Airtightness test: test speed 333Amp/min
- Foreign material test: perform foreign material test using automatic foreign material tester (P4-1027), the foreign materials were visually checked and recorded for the defective items.

※ In the manufacturing process, the stirring speed was checked, and the pH of the preparation was checked. However, after completion of the stirring operation, a verification procedure such as visual inspection of whether dissolution and mixing of the manufactured solution was adequately homogeneous. It was necessary to record and manage in the manufacturing record.

※ Open-RABS was installed and operated to manage the working environment during filling, but it was necessary to conduct a leak test on the gloves to block the possibility of contamination through the installed gloves.

○ Gemcit injection (Gemcitabine Hydrochloride) manufacturing order and record

- Manufactured number: GC1803003, GC1808004, GC1811005
- Manufactured date: 2018.03.13., 2018.08.12., 2018.11.28.
- Manufactured unit: raw material weighing → direct materials washing and sterilization → manufacturing → filtering → filling and anti-tilting → freeze drying → capping → exterior washing → packing
- Autoclave steam sterilizer: Ring and Vat used during freeze drying were used after being autoclave steam sterilizing, sterilize temperature over 121℃, 20 minutes, loading pattern being recorded in manufacturing record.
- Before O-RABS was used, leak test was performed on gloves and used if suitable. Leak test was performed again after use.
- 70% ethanol and IPA were used in turn every month as disinfectants, after being sterilized filtered, and spray gun was used after being sterilized.

- Filling instruments were separately sterilized before use, have and check the list.
- Capsule type filter was used for filter machine, performing completeness test (over 3200mbar) before and after the use, and used as disposable.
- Bioburden test was performed every manufacturing unit.
- At the time of bottle washing, regeneration water and injection water were used to wash, and silicone fluid (35% Dimethicone NF Emulsion) was added to the vials.
- Vials were tunnel sterilized after being washed, set as 320±15℃, and set as 150mm/min (set value).
- Before manufacturing, manufacturing room was using anticancer agent main ingredient, filler, etc. after weighing them in separate booth.
- pH and conductivity were measured for manufacturing water before use.
- 4mL (3.92~4.12mL) was filling about, filling speed was 65±5V/min, and performed freeze drying by putting into the freeze dryer after filling.
- Complete after freeze drying, after capping, foreign material test and airtightness were performed, exterior being washed with injection water after capping.
- Manufacturing order record present about packing process, the contents of material dispatch, usage record, process yield, etc. were recorded for packaging, and sample of materials is stored.

Deficiency

☐ Complement the following regarding test manufacturing process management:

○ Semi-finished products need to have proper test inspection after completed process to have homogeneity of the product.

- In the manufacturing process, the stirring speed was checked, and the pH of the preparation was checked. However, after completion of the stirring operation, a verification procedure such as visual inspection of whether dissolution and mixing of the manufactured solution was adequately homogeneous. It was necessary to record and manage in the manufacturing record.

○ For Open-RABS used during filling work, it needed to be managed to fulfill environmental condition.

- Open-RABS was installed and operated to manage the working environment during filling, but it was necessary to conduct a leak test on the gloves to block the possibility of contamination through the installed gloves.

○ In the manufacture of anticancer injection drugs, it is necessary to pay attention to the contamination of microorganisms and to maintain the clean grade.

- Rubber cap sterilized during anticancer building manufacturing process pass through Grade B area, confirming the quality of the product is maintained by arriving filling machine in Grade A area without contamination prevention process, and create process to prevent microorganism contamination.

※ Rules for the Safety of Pharmaceuticals [Appendix 1] 8.1 Manufacturing Process Control

9)	Production hygiene management	Production

Key checklist

☐ Worker's hygiene

○ Individual's hygiene management rule
- Document number: SOP-03E-0001, confirmation date 2017.5.23.
- Individual's hygiene management chart was created and managed for workers, and medical examination was performed regularly.
- Excluded from the work if health is abnormal and washing and disinfection was performed when entering workstations.

☐ Workstation hygiene

○ general injection workstation cleaning rule
- Document number SOP-03B-4001, confirmation date 2018.5.9.
- Each workstation's cleaning method, cleaning cycle, type of water and detergent used, disinfectants management, cleaning status confirmation process, corrective action if deviant, etc. were regulated.

○ Manufacturing process of disinfectants
- Document number: SOP-14B-0007
- 70% ethanol, 70% isopropanol: used for disinfection of goods, hand disinfection, floor and wall disinfection.
- 0.1% Benzalkonium chloride: used as aseptic room ceiling and wall cleaning.
- Ethanol and isopropanol was used in tern every month, filtered with 0.2㎛ filter and stored, and disinfectants storage period after manufactured was 1 week.
- Manufacturing and filtering record were recorded in disinfectants manufacturing and filtering record.

○ Real-time floating particles monitoring system operation (general) (SOP-05A-0022, 1, 2018.10.15.)
- Real-time floating particles measurements were performed from facility set up through completion of final manufacturing process. Alert and action level were set and managed when alarm occurs.
- Instruments were set and managed to print starting time and finishing time in floating particles data.

○ Manufacturing method of disinfectants SOP (SOP-14B-0007, 10, 2019.02.01.)
- Storing container material of disinfectants were PP (Polypropylene), material that can be sterilized, can be used by sterilizing at 121℃, 20minutes, and can be used up to 50 times based on report.
- Use period of disinfectants were 1 week, so it was used for a year by setting period by guessing use period of 50 times every week.
- Spray was used after sterilization.

☐ Manufacture hygiene management standard document

○ Content solidifying system working clothes management rule (document number: SOP-03A-1005, performed date: 2017.3.20.)

- Regular revision was on 2017.3.13., regulating workers' and foreigners' working clothes based on cleanliness.
- Regulated detailed process on working clothes collection, return, main washing, etc.
- Objects that need to be washed in Grade D workstation was washed within 24 hours, and within 48 hours during weekend.

Deficiency

○ Not applicable.

10)	Raw material and product management	Production/distribution and shipment

Key checklist

☐ Storage management

○ Raw/material storage management rules (SOP-08A-0003, 07, 2017.02.27)

- Regulated raw/material receipt and receipt inspection, confirm supplier approval, receipt inspection, raw/material transport and test request, storage management according to suitability judgment, appropriate raw/material storage management, check the quality of raw materials in long term storage, release management of raw/materials, storage management of semi-finished and packaged finished products, product shipment management, return processing.
- Person in charge for storage management managed ingredient receipt, stored and released for storing and manufacturing with ERP, recording temperature and humidity at specified intervals and checked storage condition.
- For raw/material being storage managed for set period after receipt, it was stated that quality management was needed through re-test rule to decide suitability of use.
- Temperature and humidity were set as raw material storage 15~25℃, RH below 65%, material storage 1~30℃, RH below 70%, anticancer agent raw material 19~25℃, RH below 60%, raw material refrigerated room 2~8℃, freezer -20~-30℃.

○ Packaged finished product receipt and storage management method SOP (SOP-08A-0015, 03, 2017.02.06)

- Regulation of receipt method of packaged finished product, sample collection method of packaged finished product, storage method of packaged finished product, location based on storage method of each temperature present.
- Stored in non-conforming storage and prescribed not to move at random for storage management of non-conforming products.

☐ Insect control regulations

○ Insect control facility inspection regulations (SOP-05B-0009, 019, 2018.04.16)
- The person in charge of insect control in production support team is designated by the person in charge of storage management, and responsible for checking and recording the mouse feed box.
- Person in charge of each department is responsible for checking and recording mouse bird lime and checking for abnormalities.
- It was regulated that insect control department of the quality assurance team confirms the regular conduct of the inspection activities of the insect prevention facilities by departments, informs the personnel of each department about the occurrence of abnormalities, and asks the consignment company to correct them, creating and responding to anomaly reports, and analyze the frequency and tendency of the inspection records of the insect control facility so that the cause can be identified and corrective actions can be implemented.
- Mouse feed box, mouse bird lime, thunder blue, blue storm (outdoor lightening insect killer), insect catching light (inner insect attract machine) were operated as insect control facility.
- August 2018 Dong-A ST Cheonan factory insect control result report was confirmed, and results of mouse bird lime, insect catching light, thunder blue, blue storm were confirmed.
- Pest Control Service Agreement between Dong-A ST corp. and Cesco corp. was confirmed.

☐ Supplier assessment

○ Audit management standards of QM team
- Document number: MAN-QM-301, confirmed date 2019.4.22
- In case of main ingredient, and primary packing material were evaluated at the time of new selection and every three years thereafter, subsidiary materials and labeling materials were evaluated every five years.
- In the case of new companies, on-site evaluation was the principle, and existing companies' risks were evaluated according to the audit set up table and deciding whether to evaluate on-site or in writing.
- Audit method was divided into written audit, on-site audit and special audit, and regular audits are based on written audits. In principle, on-site audits were prescribed for new companies, but if necessary, they could be selectively conducted.
- It describes the procedures for notifying the audit plan, the composition of the audit team and the preparation of the audit report. Criteria grades are classified into Critical, Major, Minor, and Recommendation according to their importance. The evaluation grades were classified into A, B, and C grades, and the C grades were required to be reevaluated after CAPA.

○ Dong-A Perdipine injection solution major raw material manufacturer evaluation result report
- Main ingredient (Nicardipine) manufacturer
    - Document number VAR-QM-RM-037, confirmation date 2018.10.10.

- Daito Pharmaceutical (Japan), which is manufacturer of Nicardipine, was newly evaluated, processing written evaluation and found to be suitable.

– Primary packing material manufacturer
  - Document number VAR-QM-PM-015, confirmation date 2018.11.22.
  - Regular inspection was performed on the laminated glass, which is used for vials for injection, ampule manufacturer, and the site was visited and evaluated, and found to be suitable.
– Secondary components manufacturer
  - Document number VAR-Q3-RM-349, confirmation date 2015.8.11.
  - Regular inspection was performed on Sanyo management, supplier of secondary component D-sorbitol, and as a result of written evaluation, it was found to be suitable.
– Secondary components manufacturer
  - Document number VAR-QM-RM-510, confirmation date 2017.7.20.
  - Regular inspection was performed on Merck KGaA, supplier of secondary components including hydrochloric acid, and as a result of written evaluation, it was found to be suitable without deficiency.

☐ Gemcit injection manufacturing company evaluation document

○ Primary packing material
– Supplier name: Laminated glass corp., 1785-15 Chungwon-ro, Wongok-myun, Ansung-si, Gyeonggi-do.
– Document number: VAR-QM-PM-015
– Supply primary packing material ampule and vial as material supplier.
– Evaluation date: 2018.11.12.
– On-site evaluation was performed as an evaluation method, and found to be suitable with Grade A.

○ Primary packing material
– Supplier name: Yungjin industry corp., 1785-15 Chungwon-ro, Wongok-myun, Ansung-si, Gyeonggi-do.
– Document number: VAR-Q6-PM-111
– Supply primary packing material rubber cap and cap as material supplier.
– Evaluation date: 2016.06.03.
– On-site evaluation was performed as an evaluation method, and found to be suitable with Grade B.

○ Main ingredient
– Supplier name: Gyeongbo pharmaceutical corp., 174 Silok-ro, Asan-si, Chungcheongnam-do.
– Document number: VAR-QM-RM-034
– Supply Gemcitabine HCL injection, Pemetrexed disodium 2.5 hydrate, Ceftizoxime sodium injection as a main ingredient supplier.
– Evaluation date: 2018.06.19.
– On-site evaluation was performed as an evaluation method, and found to be suitable with Grade A.

○ Filler
– Supplier name: Merck KGaA, Frankfurter str. 250, 64271, Darmstadt, Germany
– Document number: VAR-QM-RM-510
– Supply Sodium Sulfate, HCL, Sodium hydroxide as main ingredient supplier.
– Evaluation date: 2017.07.18.
– Written evaluation was performed as an evaluation method and found to be suitable.

○ Filler
- Supplier name: ROQUETTE, Roquette Freres 1 rue de la haute loge 62136 lestrem France
- Document number: VAR-QM-RM-507
- Supply D-mannitol as main ingredient supplier.
- Evaluation date: 2017.02.14.
- Written evaluation was performed as an evaluation method and found to be suitable.

○ Filler
- Supplier name: SIGMA-ALDRICH Co., Ltd.,
- Document number: VAR-QM-RM-512
- Supply Sodium Acetate Hydrate as main ingredient supplier.
- Evaluation date: 2017.08.11.
- Written evaluation was performed as an evaluation method and found to be suitable.

Deficiency

☐ Complement the following regarding storage management:

○ Detailed procedures need to be established to confirm the completion of the test when constructing the data of the raw material receipt test inspection program.
- Raman or NIR data base was being constructed for newly received raw material Spectra blend white. The program could not print completion of verification inspection label during constructing new data, so it was stored in raw material suitable storage without completion of verification inspection label. Related standard did not include detailed process such as attaching completion of verification inspection label when new raw material is received.

※ Rules for the Safety of Pharmaceuticals [Appendix 1] 10.2 Storage Management

11)	Complaints and product recall	Complaints and product recall

Key checklist

☐ Complaints and recall

○ Product claim processing regulations (document number: SOP-12A-0001, enforcement date: 2017.5.1.)

- Amendments have been made to add risk rating assessment, add and dispose of claim recalled products and record methods, and add forms.
- The time required to prepare a response was set according to the types of claims, such as damage, insufficient capacity, foreign substance mixing, and consigned / imported products.
- The Complaint Committee was formed to deal with issues related to product complaints and product recall.
- Complaints handling process was product complaints received from customers → request for product complaint analysis to quality control office → submission to QA Office → introduction to Complaint Center Committee → cause analysis, preventive measures → introduction to Complaint Committee → fill out product complaint table → product complaint handling table delivered to customer satisfaction room → deliver processing results to customer

Deficiency

○ Not applicable.

12)	Change management	Change control

Key checklist

☐ Change management

○ Change management (document number: SOP-20A-0001, enforcement date: 2017.5.22.)

- 2017.5.8. There were document revisions such as adding the responsibility and authority team leader, changing the classification example according to the importance, reviewing the change request, and changing the contents of the team leader and method.
    - In case of Level 1, the revision of manufacturing records and the change of form have been changed to simple manufacturing records and test specifications, and the change example regarding the deletion of the revision of Level 2 test specification has been revised.
- The history of change of Level 2 and 3 or higher was checked. We confirmed the change completion report as follows.
- In case of exceeding the deadline, it is required to check the completion of change on a monthly basis, after confirming that the change was completed, the change completion report was prepared, and It is required to specify the reason for the change completion report.
- If deadline was indicated as N/A, 6 months after approval, the change was checked, and if the change is in progress, it is checked quarterly and a report is completed when change is completed.

○ Change completion report (management number: 20170720-1)

- Suitability approval completed in October 2018 regarding injection aseptic workstation real-time floating particles measuring instrument installment and system change.
- Verification and checklist: validation (environment monitoring, CSV), suitability test, related document revision

○ Change completion report (management number: 20170711-1)

- Suitability approval completed in October 2017 based on general, anticancer injection crude liquid transfer system change.

- Verification and checklist: validation (environment monitoring, compressed air test), related document revision
    - Sart created 3 new oil-free points for crude liquid transfer in response to Advanta pass changes, and revised related documents including Advanta pass operation method (document method: SOP-06B-4109), related product manufacturing record order, product standard.

○ Change completion report (management number: 20180510)

- With change request regarding LIMS & RWS program regular improvement, suitability approval completed in June 2018.
- Confirmed standard product management standard SOP revision, CSV perform.

Deficiency

○ Not applicable.

13)	Self-inspection	Self-inspection

Key checklist

☐ Self-inspection

○ GMP self-inspection standard (document number: SOP-19A-0001, enforcement date: 2017.09.18.)

- 2017.9.4. In accordance with the transfer of the self-inspection service, the detailed work procedures of the self-inspection have been revised to the GMP self-inspection standard (document number: MAN-QM-201).

○ GMP self-inspection standard (document number: MAN-QM-201, enforcement date: 2017.10.10.)

- The annual self-inspection plan is prepared within 1 quarter, and the production manager made final approval on the self-inspection plan and results.
- Schedule changes were possible within the planned quarter due to institutional inspection.
- The self-inspection team members should be retrained if necessary after five years or more, and completed when they receive 80 points or higher as a result of the training evaluation.
    - If below 80 points as a result of training evaluation, provision of one-time retraining and retest.
- Regular self-inspection is required at least once a year by industry / type and to prepare a report of self-inspection within 3 working days after completion of inspection.
- Deficiencies were classified with 4 levels, which are Critical (A), Major (B), Minor (C), Recommended (D).

○ Self-inspection record confirmation

- 2018.2.1. ~ 2018.12.31. 4 times a year
- 1st quarter (2018.3.14. ~16.): performed self-inspection related to injection production and quality, total of 104 deficiencies occurred including 5 Major issues, and all deficiencies were successfully action completed on 2018.11.5.
- 2nd quarter: Clinical drug production and quality related

- 3rd quarter: content solidifying system and quality related
- 4th quarter (2018.11.29.): self-inspection was performed on packing and quality of imported pharmaceuticals, 22 deficiencies occurred including 8 Major issues, 2019.4.22. one point was not completed in the first action status report and was to be reviewed later.

Deficiency

○ Not applicable.

14)	Education and training	Education and training

Key checklist

□ Wkers education and training

○ Education training management regulation (document number: SOP-15, enforcement date: 2019.04.01.)

- New employee OJT training is conducted in accordance with the training program I, and the education contents of each department were prescribed.
- When new employee OJT training is completed, depending on the training result, additional education and full retraining can be provided, and the result should be written on the personal history card.
- Confirmed 2018 plan during departmental GMP training.
    - We confirmed the quarterly GMP training and evaluation results report for Quality Assurance Team 1, Production Support Team, and Production Team 3, and all attendees were above the evaluation criteria.

Deficiency

○ Not applicable.

15)	Problems related to the evaluation of an application for manufacturing sale permit (report) or import item permit (report)	Question raised relating to the assessment of a marketing application e.g., Pre-authorization inspections

◯ Not applicable.

16)	Other identified unusual issues (issues)	Other specific issues identified e.g., Relevant future changes announced by company

◯ Not applicable.

17)	Manufactory assessment	Assessment of SMF if any; date of SMF

◯ Not applicable.

9. Other [Miscellaneous]

○ Animal management: not applicable
○ Genetically modified organisms management: not applicable
○ Other: not applicable

10. Deficiency [List of Deficiencies classified into critical, major and others]

■ Major: 1 item

□ Complement the following regarding stability test (1)
○ After each year, at least one manufacturing unit for each content and type of packaging of the same material as the commercially available product shall be subjected to the post-marketing stability test. In addition, make sure that the product quality is maintained during the use period or the expiration date for 8 items including Co-Apurtan tablet 300/12.5mg that have not been subjected to post-marketing stability tests and come up with measures to prevent recurrence.

- Based on own company standard document 'stability test management standard (document number: SOP-09A-0001)', post-marketing stability tests should be conducted from January to December of the relevant year as of the packaging date, but 8 items including Co-Aprutan tablet 300/12.5mg, and Dong-A Nicetile tablet were manufactured (packaged) and not tested for post-marketing stability.
  - Dong-A Nicetile tablet, Varosartan tablet 80mg, Co-varosartan tablet 80/12.5mg did not perform post-marketing stability test in 2016, Co-Apurtan tablet 300/12.5mg, Apurtan tablet 150mg, Co-varosartan tablet 80/12.5mg, Apurtan tablet 300mg did not perform post-marketing stability test in 2017, Olsartan tablet 20mg, Dong-A Perdipine Long Acting SR capsule 40mg did not perform post-marketing stability test in 2018.

※ Rules for the Safety of Pharmaceuticals [Appendix 1] 7.2 Stability Test

■ Other: 4 items

□ The following items should be supplemented with regard to environmental management (general injection) (1)
○ For the environmental management of general injection workplaces, it was necessary to establish procedures to prevent the environmental management of injection water room and contamination by workers.

- Although the injection water room was located inside the general injection workplace and managed to grade D in cleanliness, the possibility that the injection production worker entering the sterile workshop after high temperature work in the main room could adversely affect the cleanliness of the general injection workshop as there were no other restrictions on maintenance work of the injection water storage could not be ruled out.

○ In order to confirm the adequacy of the HEPA filter installed in the clean booth, it was necessary to indicate and manage the initial differential pressure when replacing.

- The HEPA filter was installed in the clean booth to manage the environment, and the differential pressure gauge was installed to check the normality of HEPA filter.

- In order to properly carry out the normal range verification procedure, the indication of the differential pressure at the time of initial installation and the differential pressure required to be replaced could not be confirmed.

○ It was necessary to properly control the differential pressure between different areas of cleanliness.

- For the environmental management of clean areas, we managed to maintain the differential pressure between cleanliness, and set the differential pressure standards to conduct regular inspections. Differential pressure between general injection hallway (C205, CNC) and raw material import room (C241, D area) was checked and recorded, but real differential pressure measured was between the hallway (C205) and the inner hallway (C242) was checked. The differential pressure could not be determined for the zone where cleanliness is changed from the CNC zone to the D zone (between hallway and the raw material import room).

○ It was necessary to properly manage the test method for the drop bacteria test and the worker surface bacteria test during environmental monitoring.

- For drop bacillus test, the test was conducted by exposing each of them separately (about 1 hour 30 minutes) during the working hours but conducting the test with continuous exposure of up to 4 hours including lunch time was needed. In the case of worker surface bacteria, only one of the workers was tested, but it was necessary to test the surface bacteria for all possible workers.

  ※ Rules for the Safety of Pharmaceuticals [Appendix 1] 2.3 Environmental Management

  ※ Regulations on Pharmaceutical Manufacturing and Quality Control [Appendix 1] 13. Process Operations

□ Complement the following with regard to test management (2)

○ Regarding the form of storage sample packaging for raw materials (primary ingredients), whether the packaging is of equivalent quality need to be confirmed.

- Dong-A Opalmon tablet's main ingredient, stored in freezer, has packaging form of glass bottle, that ingredient reference sample container PE, differ from one another, but the sample storage container material could not be confirmed to be equivalent or more than equivalent to the final packing material.

  ※ Rules for the Safety of Pharmaceuticals [Appendix 1] 7.1 Test Management

☐ Complement the following regarding test manufacturing process management (3)

○ Semi-finished products need to have proper test inspection after completed process to have homogeneity of the product.

- In the manufacturing process, the stirring speed was checked, and the pH of the preparation was checked. However, after completion of the stirring operation, a verification procedure such as visual inspection of whether dissolution and mixing of the manufactured solution was adequately homogeneous. It was necessary to record and manage in the manufacturing record.

○ For Open-RABS used during filling work, it needed to be managed to fulfill environmental condition

- Open-RABS was installed and operated to manage the working environment during filling, but it was necessary to conduct a leak test on the gloves to block the possibility of contamination through the installed gloves.

○ In the manufacture of anticancer injection drugs, it is necessary to pay attention to the contamination of microorganisms and to maintain the clean grade.

- Rubber cap sterilized during anticancer building manufacturing process pass through Grade B area, confirming the quality of the product is maintained by arriving filling machine in Grade A area without contamination prevention process, and create process to prevent microorganism contamination.

※ Rules for the Safety of Pharmaceuticals [Appendix 1] 8.1 Manufacturing Process Control

☐ Complement the following regarding storage management (4)

○ Detailed procedures need to be established to confirm the completion of the test when constructing the data of the raw material receipt test inspection program.

- Raman or NIR data base was being constructed for newly received raw material Spectra blend white. The program could not print completion of verification inspection label during constructing new data, so it was stored in raw material suitable storage without completion of verification inspection label. Related standard did not include detailed process such as attaching completion of verification inspection label when new raw material is received.

※ Rules for the Safety of Pharmaceuticals [Appendix 1] 10.2 Storage Management

11. Recommendations [Recommendations]

○ Not applicable.

12. Summary and conclusions [Summary and conclusions]

○ Overall [Appendix 1], it is judged that the product is manufactured according to the pharmaceutical manufacturing and quality control standards, but part of the lack of corrective • supplementary findings were identified and corrective • supplementary measures were requested.

- No critical deficiencies, 1 major deficiency, and 4 other deficiencies.

[Reference 1]

Definition of Deficiency

1. Critical deficiency

Points that have produced or are at significant risk of producing products that can produce harmful residues in the body of animals used as food or product that is harmful to humans or animals

2. Major deficiency

Not critical, but deficiency relevant to one of the below.

○ Items that are inconsistent with the permit were manufactured or may be manufactured.

○ Item indicating important deviance from PIC/S GMP.

○ Item indicating important deviance from product approval condition (in PIC/S).

○ Items indicating that there is a problem with the manufacturing unit approval process or that the person in charge is performed the duty wrong.

○ Not an major deficiency, but other errors combined with several other errors. (could be major error if accumulated, so explain and report as important deficiency)

3. Other deficiency

Not classified as crucial deficiency or important deficiency, but deficiency that deviated from GMP. (classified as others due to minor issue or insufficient information to be classified as important or crucial)

DEFINITION OF DEFICIENCIES TO BE USED IN PIC/S INSPECTION REPORT

1. CRITICAL DEFICIENCY

A deficiency which has produced or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2. MAJOR DEFICIENCY

A non-critical deficiency;

Which has produced or may produce a product, which does not comply with its marketing authorization: or which indicates a major deviation from PIC/S Good Manufacturing Practices: or (within PIC/S) which indicates a major deviation from the terms of the manufacturing authorization: or which indicates a failure to carry out satisfactory procedures for release of batches or (within PIC/S) a failure of the authorized person to fulfil his/her required duties: or a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

3. OTHER DEFICIENCY

A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical)