DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, CDER Inspection Assessment Branch 10903 New Hampshire Avenue Bldg. 51, Room 4316 Silver Spring, MD 20993 Phone: 1-301-796-3254 Industry Information: www.fda.gov/oc/industry	May 22-26 and May 29-June 2, 2017 FEI NUMBER 3005241015

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Myung Keun Oh, Senior Vice President of Global Quality, Operation Division

FIRM NAME	STREET ADDRESS
Celltrion Inc.	23 Academy-ro, Yeonsu-gu
CITY, STATE AND ZIP CODE	**TYPE OF ESTABLISHMENT INSPECTED**
Incheon, 22014, Republic of Korea	Sterile Injectable Drug Product and Drug Substance Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION #1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has already been distributed.

1. Since the fourth quarter of 2015, 140 complaints have been received for difficult (b) (4) because of no (b) (4) in the vials of (b) (4) Vials are stoppered at the (b) (4) of (b) (4) (b) (4) with (b) (4) Document GP2-FF-16-059 states: "The purpose of (b) (4) step is (b) (4) (b) (4) into vials to prevent the (b) (4) Another purpose is convenience of users during (b) (4) "

Investigations confirmed the complaints and identified a root cause of stoppers (b) (4) the (b) (4) The (b) (4) the stopper allowing for ingress of (b) (4) instead of a (b) (4) Adequate corrective and preventive actions have not yet been implemented to address already released product, eliminate the root causes for on-going manufacturing, and ensure that vials without (b) (4) can be detected and removed prior to the release of batches.

The investigations have not been thorough and timely:

a. Yield investigation DE-P2-15-051 dated 14 April 2015 identified (b) (4) stoppers during (b) (4) unloading as a root cause. It identified (b) (4) stoppers as an ongoing occurrence. Enhanced (b) (4) cleaning corrective actions were not evaluated for effectiveness in eliminating the (b) (4) stoppers. Production personnel reported to QA an even larger frequency in the observation of stopper (b) (4) during (b) (4) unloading in quarter four of 2015. QA confirmed they were informed of this issue, but there is no QA documentation of this communication. Deviations DE-P2-16-073 from 25 May 2016 and DE-P2-16-116 from 09 August 2016 documented yield deviations and described ongoing problems related to (b) (4) stoppers during (b) (4) unloading.

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b. No study has been conducted to determine the interaction of the stoppers and the (b) (4) that impact the (b) (4)

c. No study has been performed to evaluate the frequency of no (b) (4) vials or to evaluate how they are distributed within the (b) (4) different (b) (4)

d. Full release and stability tests have not been performed on vials without (b) (4) For example, (b) (4) content, (b) (4) time, color and clarity (b) (4) or particles (b) (4) have not been evaluated for vials without (b) (4)

e. Only (b) (4) vials without (b) (4) from (b) (4) batch, (b) (4) have been tested for (b) (4) using peptide mapping.

f. A sensor is installed to reject vials with (b) (4) stoppers. This sensitivity of the sensor to reject vials with (b) (4) stoppers has not been thoroughly evaluated.

g. An inadequate blowback feature of vials has been identified as a potential cause for (b) (4) However, the blowback feature on vials without (b) (4) has not been evaluated.

h. Corrective actions taken have not been thoroughly evaluated for effectiveness before or after implementation:

The production department initiated change control CC2-15-164 to increase the (b) (4) of the (b) (4) for the (b) (4) There was no documented evaluation of how much (b) (4) was necessary prior to approving the change. The action was ineffective and an addendum was initiated to again increase the (b) (4) This was still unsuccessful in preventing (b) (4) (b) (4) were installed per change control CC2-16-132. There was no evaluation to determine whether the (b) (4) were effective in reducing vials without (b) (4)

Change control CC-15-194 was initiated to implement the use of (b) (4) stoppers. No evaluation was performed to evaluate the effectiveness of this change to reduce (b) (4) and eliminate vials with no (b) (4)

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during the subsequent process validation studies conducted with the new stoppers. A study of (b) (4) volume was later performed for batch (b) (4) but was limited to (b) (4) vials. Further, there is no requirement that the (b) (4) stoppers be used instead of non-(b) (4) stoppers for ongoing production.

2. Investigations into foreign matter detected in drug product and drug substance are not investigated in a timely manner.

a. On 03 February 2017 and 08 February 2017 Celltrion was informed by a contract laboratory of an OOS for particles in (b) (4) batch (b) (4) and (b) (4) respectively. These batches had been released for packaging and labeling. The samples were returned to Celltrion on 14 February 2017. Identification was not completed until 28 February 2017 when it was confirmed that the particles consisted of (b) (4) fibers. Deviation DE-P2-17-042 was not opened until 28 February 2017.

No further action was taken until additional samples were requested from the secondary packaging site on 29 March 2017. Samples were received at Celltrion for further evaluation on 13 April 2017. As of 31 May 2017 none of these samples has been evaluated for foreign particles, no investigation has been performed into the root cause of the (b) (4) fibers, and the investigation remains open.

b. On 16 March 2017 a stability sample at the one month time point from lot (b) (4) of (b) (4) drug substance was found to have "Too Numerous To Count" particles against a limit of less than or equal to (b) (4) for proteinaceous particles. On 20 March 2017 some of the particles were identified to be (b) (4) a foreign particle that failed the specification of (b) (4) visible foreign particulate. No OOS investigation was opened until 21 March 2017. As of 31 May 2017 no investigation has been performed into the root cause of the failure and the investigation remains open.

c. On 13 April 2017 a stability sample at the two month time point from lot (b) (4) of (b) (4) drug substance was confirmed to have a foreign particle. These particles were later identified to be (b) (4) An OOS investigation was not opened until 12 May 2017 and a deviation investigation was not opened until 16 May 2017. As of 31 May 2017 no investigation has been performed into the root cause of the foreign particle and the investigation remains open.

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d. Particles detected during visual inspection have not been evaluated to determine their source. For example, the source of particles identified as "(b) (4) , seen in multiple 2017 batches, has not been identified. Further, the reject vials from actual production have not been incorporated into the visual inspection training and qualification kit.

3. Investigations of unexpected trends in the environmental monitoring data are not investigated thoroughly and in a timely manner.

a. The (b) (4) trending report for the environmental monitoring of Plant # (b) (4) for (b) (4) had not been completed as of 31 May 2017. Trending procedure QC1031 "Trend Analysis of Environmental/Clean Utility Monitoring" states that completion of the (b) (4) trend report is "recommended" by the (b) (4) of the (b) (4) . The data from (b) (4) showed a higher level of excursions compared to (b) (4) and it was reported by QC personnel that a CAPA was necessary for the abnormal trend. However, no CAPA has been initiated as of 31 May 2017 to address the (b) (4) trend. The (b) (4) data has shown the excursions are occurring at an even higher rate than in (b) (4)

b. Review of trending of the environmental monitoring data does not ensure changes in the microbial flora are detected and evaluated. The (b) (4) trending for Plant # (b) (4) showed no mold organisms were recovered. From 22 February 2016 to 21 May 2016 mold organisms were recovered in the ISO 7 areas six times, five of which were Aspergillus species. No investigation was performed to identify the source of the mold organisms.

OBSERVATION #2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

During set-up and filling of batch (b) (4) of (b) (4) on 23 May 2017:

1. An operator was observed to perform an intervention during filling to remove a jammed stopper by reaching over the exposed stoppers in the stopper bowl with the Restrictive Access Barrier system (RABS) (b) (4)

2. During set-up, the operators were observed to reach over exposed sterile surfaces including the stopper bowl and the (b) (4) of the stopper (b) (4) with their hands and arms.

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3. The (b) (4) to the RABS was left open unnecessarily while operators obtained new wipes for sanitization at the (b) (4) of the equipment set-up.

4. The quality unit does not provide oversight of aseptic production operations that occur during (b) (4) work (b) (4)

OBSERVATION #3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

1. During media fills performed to validate the aseptic filling process, integral media filled vials are rejected. They are not incubated as described in media fill procedure (b) (4) 2205 "Media Fill Plan for Sterile Injectable Products"

a. Media fill (b) (4) 19 vials were rejected for "fallen at the conveyor" during unloading of the (b) (4) These vials were stoppered and integral and are not required to be rejected during routine operations as described in procedure FF23010 "Operation of Filling Machine RABS".

b. In both media fill (b) (4) and (b) (4) media filled and stoppered vials were rejected during simulation of a power failure at the capping station.

c. Media fill (b) (4) 5 media filled vials were rejected due to gross weights out of range.

d. Media fill (b) (4) 2 vials were removed during the unloading of the (b) (4) with no assignable root cause.

2. Personnel are permitted to enter the filling and (b) (4) room during aseptic operations based on gowning qualification. They are not required to participate in a media fill. Further, there is no effective system to identify which personnel have entered the filling room.

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3. The media fill procedures do not require (b) (4) of the media fill vials (b) (4) of incubation.

4. There is no documentation of the personnel that participate in the reading of the media fill units, no qualification for the personnel that read the media fill units, and no procedure describing the techniques for reading the media fill units.

5. No dynamic airflow studies (e.g., smoke studies) have been performed to demonstrate unidirectional airflow and to determine risk to product sterility throughout the RABS area. Only points along the path where (b) (4) vials travel were included in the study instead of covering the entire RABS area. The studies did not include routine aseptic interventions such as set-up activities or removal of jammed stoppers. The smoke generated was not sufficient to demonstrate airflow of the evaluated areas.

OBSERVATION #4

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

1. At the end of incubation on 23 May 2017 settle plate samples (b) (4) collected from filling room (b) (4) during the aseptic filling of batch (b) (4) were observed to have (b) (4)

2. Active volumetric air sampling is not included in the environmental monitoring program for the aseptic filling areas during dynamic filling operations.

3. The surface monitoring of the ISO 5 areas of the (b) (4) area is performed (b) (4) operations occur, but not after. The active air and non-viable particle monitoring occur (b) (4) operations, not during dynamic operations.

4. No personnel monitoring frequency has been established for personnel that are not directly involved in filling operations, but enter the filling and (b) (4) room during production operations.

5. The locations for surface monitoring are not described in written procedures with enough detail to ensure reproducible sampling.

6. Production personnel perform the environmental monitoring and personnel monitoring. There is no required

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oversight of these activities by the quality unit.

OBSERVATION #5

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

1. Results of disinfectant efficacy studies were not used in the establishment of disinfectant use schedules in Plant (b) (4) For example:

a. Disinfectant (b) (4) is used as the only equipment disinfectant for the ISO 7, 8, and 9 areas for (b) (4) The disinfectant failed the acceptance criteria for all surfaces against the organisms Staphylococcus aureus, Candida albicans, Aspergillus brasiliensis, and Micrococcus luteus.

b. Disinfectant (b) (4) is used as the only disinfectant for walls and ceilings on (b) (4) . The disinfectant failed the acceptance criteria for Aspergillus brasiliensis on 8 of (b) (4) surfaces, including "(b) (4) paint on (b) (4) Wall". Disinfectant (b) (4) is used as the only disinfectant for walls and ceilings on (b) (4) (b) (4) The disinfectant failed the acceptance criteria for "(b) (4) paint on (b) (4) Wall" for Staphylococcus aureus, Candida albicans, Aspergillus brasiliensis, and Micrococcus luteus.

No action was taken to ensure there was an effective disinfectant used on the walls for mold. The (b) (4) EM trending identified mold was recovered in the ISO 7 areas eight times, including five that were Aspergillus species.

2. The disinfectant efficacy studies did not include surfaces that are disinfected and left in place (b) (4) batches in the critical areas. For example (b) (4) used for the filling machine format parts and (b) (4) (b) (4) used for the exterior of the filling pumps.

3. The air intake vents located in the ISO 7 area for the laminar flow hood used for (b) (4) and fill of the drug substance had visible dust build-up on their surfaces.

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OBSERVATION #6
Equipment used in the manufacturing areas of a drug product is not of appropriate design.

1. Calibration tags on the non-viable particle counters inside of the filling RABS are attached with beaded chains.

2. Identification numbers for format parts are taped onto equipment surfaces inside the filling RABS.

OBSERVATION #7
Failure to demonstrate that your manufacturing process can reproducibly manufacture drug substance meeting its predetermined quality attributes.

Process validation studies for the drug substance (b) (4) did not establish scientifically sound sampling plans to evaluate intra batch variability.

This is a Repeat Observation from the March 2015 FDA 483.

OBSERVATION #8
Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Failing filter integrity test results are not reported as required by procedure MO1040 "Operation and Maintenance of Filter Integrity Tester". After failures, the tests are repeated without documenting the failing results, the actions taken, or the reasons for invalidating the original results. For example:

1. The (b) (4) Filter lot # (b) (4) failed the bubble point test at (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) on 24 March 2017. The test passed at 2:45 on 25 March 2017. Only the passing result was reported.

2. The (b) (4) Air filter lot # (b) (4) failed the water intrusion integrity test at 9:52, 10:20, (b) (4) , and (b) (4) on 17 May 2017. The filter was instead tested according to bubble point on 17 May 2017 at (b) (4) with a passing result. Only the passing result was reported.

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OBSERVATION #9

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

1. Operation personnel share a common username and password to access the Sartocheck4 Filter Integrity Tester unit 0034202581. The electronic data can be deleted and the audit trails are not reviewed.

2. Operation personnel share a common username and password to access the UV Visible Spectrophotometer SPM-2802. The electronic data can be deleted and the audit trails are not reviewed.

3. Specific procedures to describe review of audit trails of the different software used have not been established.

OBSERVATION #10

Procedures for the preparation of master production and control records are not followed.

There was no system to track the issuance and use of all laboratory raw data forms, such as microorganism identification forms described in QC-4004. Laboratory personnel had access to blank electronic forms for printing without control. Controls for these forms were scheduled to be implemented 26 May 2017. However, these new controls did not apply to all forms that capture original GMP data, for example form QC0046-F1 "Audit Trail Inspection and Abnormal Finding Reporting". Additionally, the QC laboratory had a document shredder that was filled with shredded documents on 22 May 2017. There is no control over the use of the shredder.

OBSERVATION #11

Data is not documented contemporaneously.

1. On 29 May 2017 vessel V1120 was filled with (b) (4) reported to be for batch (b) (4) of (b) (4) media. The batch record entries for (b) (4) addition as well as previous batch record steps for the area clearance, equipment cleanliness verification, and the verification of (b) (4) had not been documented.

2. On 29 May 2017 batch record (b) (4) for Cell (b) (4) had no entries for the (b) (4) (b) (4) in step (b) (4) It was reported that this step had been completed the previous (b) (4)

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3. Collection times of environmental monitoring samples are not recorded at the time samples are taken. General times are recorded to represent multiple samples in multiple areas.

OBSERVATION #12

Batch production records do not contain complete information relating to the production and control of each batch.

The production personnel in Plant #(b)(4) use computers located within the production area to create unofficial records of the production activities. These unofficial records are not described by any procedure or reviewed. The unofficial records contained information that was not captured in the official batch records. For example:

1. An unofficial spreadsheet documenting preparation of the (b)(4) media (b)(4) documented it was necessary to use a (b)(4) (b)(4) These comments were not reflected in the official batch record.

2. The unofficial spreadsheet for (b)(4) media (b)(4) documented the use of a bench top (b)(4) for batch (b)(4) because the installed (b)(4) was not providing accurate results. This is not reflected in the official batch record.

3. The unofficial spreadsheet for (b)(4) contains notes for slow (b)(4) due to (b)(4) clogging. This is not reflected in the official batch record.

4. The unofficial spreadsheet for (b)(4) media (b)(4) contains measurements from bench top (b)(4) It was reported that the production personnel do this because the installed (b)(4) are not always reliable. The bench top values are not recorded in the official record and no investigation into the unreliability of the installed (b)(4) (b)(4) to implement corrective actions has been initiated.

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