Celltrion Inc. 1/26/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-28

January 26, 2018

Mr. Woo Sung Kee
President
Celltrion, Inc.
23 Academy-ro, Yeonsu-gu
Incheon, 22014
Republic of Korea

Dear Mr. Kee,

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Celltrion, Inc. at 23 Academy-ro, Yeonsu-gu, Incheon, from May 22 to June 2, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's June 22, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Poor Aseptic Behavior
On May 23, 2017, our investigator observed multiple poor aseptic practices during the set-up and filling of **(b)(4)** batch **(b)(4)**.

For example, during the aseptic filling of vials, an operator used restricted access barrier system (RABS) **(b)(4)** to remove a jammed stopper by reaching over exposed sterile stoppers in the stopper bowl. The RABS **(b)(4)** disrupted the unidirectional airflow over the stopper bowl, creating a risk for microbial contamination. After the operator removed the jammed stopper, the filling line was restarted, but the affected stoppers were not cleared.

In your response, you included revised aseptic technique procedures for set-up and filling. However, your response was inadequate because you did not perform a retrospective investigation and thorough risk assessment of the effect on your product. In addition, your revised procedure FF21024 permits contamination of product-contact surfaces during set-up, followed by wiping with a disinfectant, instead of preventing sterile equipment contamination by improved design and procedures.

In response to this letter, provide:

- Your plan to assure appropriate aseptic practices and cleanroom behavior during production. Include specific steps to ensure routine supervisory oversight for all production batches. Also describe the frequency of quality assurance oversight (e.g., audit) during aseptic processing and other operations.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior such as that observed during the inspection may have affected quality and sterility of your drugs.
- A corrective action and preventive action (CAPA) plan to fully remediate any contamination hazards to sterile product contact surfaces during set-up, including improved equipment design and procedures.
- A standard operating procedure (SOP) that requires routine sterilization of your RABS **(b)(4)** and specifies maximum use time.
- Comprehensive identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow (e.g., RABS material transfers).
- A CAPA plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will improve aseptic processing operation design, control, and personnel qualification.

Smoke Study Deficiencies
Our investigator reviewed the smoke studies for the RABS filling and **(b)(4)** loading areas, and documented deficiencies. The smoke studies conducted for these ISO 5 areas lacked sufficient evaluation of dynamic conditions, including set-up and routine aseptic manipulations. For example, you did not address critical interventions such as the removal of jammed stoppers, so it was not possible to evaluate the effects of such interventions on unidirectional airflow.

In your response, you stated that you conducted two additional smoke studies. In response to this letter, provide a copy (e.g., an mpeg file) of your new smoke study recordings.

Media Fill Deficiencies
Our investigator observed multiple deficiencies related to the validation of your aseptic processes.

a. Our review of your media fill batch records found that your firm rejected integral vials. For example, during simulation of a power failure at the capping station, your firm rejected integral vials filled and stoppered prior to the power outage. The practice is inappropriate and contrary to your firm's media fill procedure **(b)(4)** 2205 *Media Fill Plan for Sterile Injectable Products*.

Clear and specific SOPs for line clearance (i.e., intervention type and quantity of units removed) enable consistent production practices and assessment of these practices during media fills. Where procedures lack specificity, there is insufficient justification for exclusion of units from the media fill batch. You should not remove more units during a media fill intervention than would be cleared during a production run. To ensure a valid assessment, it is critical that media fill studies accurately simulate these and other worst-case conditions encountered during commercial production.

b. Your procedure **(b)(4)** 2205 did not specify that all personnel authorized to enter the aseptic processing rooms during manufacturing should participate in a media fill at least once a year.

c. You lacked adequate procedures for training and qualifying personnel to examine media filled units following incubation, and you did not specify how they are to conduct this inspection. Furthermore, you did not keep adequate records that document which personnel performed the examinations.

In your response, you included revised media fill procedures, and indicated that you performed an additional media fill. However, you did not adequately address the vials that were erroneously removed and the impact on the accuracy of past media fill results. You also failed to perform a full assessment of your media fill program. For example, you did not conduct a thorough assessment of the training and qualifications of personnel to determine whether they can reliably examine media fill units.

In response to this letter:

- Provide a retrospective assessment of all media fills since January 2014. List all media fills conducted, fill date, number of units runs, number of vials rejected, number of units incubated, and number of positive units. Describe the circumstances under which any integral media fill vials were removed from each media fill batch. Explain in detail why they were rejected. Provide the final, signed summary report prepared by your firm for each media fill.
- Describe how you revised SOPs to specify when units must be rejected during commercial operations. Provide your full CAPA to ensure that units can be rejected in media fills only if appropriate and consistent with corresponding production SOPs.
- Provide a comprehensive independent review of your media fill program.
- List all batches processed during power outages since January 2015. Describe actions taken after the power failures to restore appropriate aseptic processing conditions. If you permitted continuation of batch production, describe how many units you rejected and the criteria you used to accept units following the power failure. Also, provide the related investigation report and an assessment of suitability of any batch that may have been exposed to a loss of environmental control in the aseptic processing facility.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Lack of **(b)(4)** *in Vials*
Our investigator documented that, from October 2015 to May 2017, you received approximately 140 complaints for **(b)(4)** related to **(b)(4)** in the vials. A substantial number of these critical complaints were for U.S. batches and were received after FDA approved **(b)(4)** in **(b)(4)**. Your investigation identified the root cause as vial stoppers **(b)(4)** which caused **(b)(4)** stoppering. This allowed **(b)(4)** to replace the **(b)(4)** in the **(b)(4)**. This defect can significantly affect multiple quality attributes of your product over its shelf life.

Your SOP QA2002 *Deviation and Corrective Action Preventive Action* requires prompt investigation and resolution of deviations. However, you investigated recurring **(b)(4)** complaints without resolution for more than two years, as indicated from the first deviation report DE-P2-16-003 dated January 6, 2015, to the summary report dated March 3, 2017.

You failed to thoroughly investigate the lack of **(b)(4)** in vials and to implement a timely and effective CAPA.

In addition, you failed to submit a biological product deviation report for **(b)(4)** to FDA as required by 21 CFR 600.14(c).

In your response, you stated that you applied **(b)(4)** on the surface of both of the **(b)(4)** and are now routinely using **(b)(4)** stoppers. You state that these changes have reduced the **(b)(4)** between **(b)(4)** and stoppers. You have also added a **(b)(4)** as a **(b)(4)** detector for in-process control testing.

In response to the letter, provide:

- An update on CAPA plans you have implemented to prevent production of vials without **(b)(4)**. Describe all steps taken to prevent recurrence of this problem. Include updated summaries of defect data from production batches, complaints (include batch number and date of manufacture), and all stability program results.
- A risk assessment that evaluates the quality and acceptability of distributed batches.
- An update on progress toward implementing in-line **(b)(4)** testing to detect **(b)(4)**.
- A comprehensive independent review and remediation of your systems used to ensure thorough and timely investigations of deviations, complaints, defects, out-of-specification (OOS) results, and failures.

Visible Particle Examination
You failed to thoroughly investigate the visible particle issues in finished drug product. For example,
a. On February 3, 2017, the contract testing laboratory you use for release testing informed your firm of two OOS results obtained during the visual particle examination of two **(b)(4)** batches, including **(b)(4)**, which was intended for the U.S. market. Your contract testing laboratory returned the samples to your firm on February 14, 2017. Although you confirmed that the particles consisted of **(b)(4)** fibers, as of your response dated November 11, 2017, you had not extended the investigation to other batches nor had you determined why you failed to detect these particles before you released the unlabeled batch of vials to your secondary packaging and labeling site.
b. In April and May 2017, you identified "**(b)(4)**" and "**(b)(4)**" foreign particles in multiple batches of **(b)(4)** for the U.S. market during your visual inspection of the **(b)(4)**. However, you did not adequately investigate these particles to determine their source, root cause, or potential effect on patients.

In response to this letter, provide:

- Your updated investigation into source, root cause(s), and impact of **(b)(4)** and **(b)(4)** particles detected in your products. Extend your investigation to other batches that may also have been compromised by the same or similar particles.
- A CAPA that establishes routine review of variations in process performance and product quality, and ensures early identification of problematic trends and related events.
- Your evaluation of the effectiveness of investigations and CAPA to remediate your firm's visual inspection program for sealed units, including pre-released vials.

3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Your environmental monitoring program for the aseptic processing (ISO 5) area was deficient.

For example, your SOP FF21017 *Environmental monitoring in operation for fill and finish process* lacked active air monitoring in ISO 5 areas during operations. In your response, you provided your updated procedures that include monitoring during manufacturing operations.

In response to this letter, describe the status of improvements you made to your environmental monitoring program and an assessment of CAPA effectiveness to ensure your program can reliably evaluate whether your aseptic processing environment remains in a state of control.

Additional Guidance on Aseptic Processing
See FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* to help you meet CGMP requirements when manufacturing sterile drugs using aseptic processing, at

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf).

CGMP Consultant Recommended
Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. In particular, the consultant should comprehensively assess your investigation and trending systems, aseptic processing line hazards, the media fill program, and the quality of batches produced for the United States. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and for ensuring ongoing CGMP compliance.

Conclusion
Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at **drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov)**, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Celltrion, Inc., 23 Academy-ro, Yeonsu-gu, Incheon, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Lixin (Leo) Xu, M.D., Ph.D.
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USA

Please identify your response with FEI 3005241015.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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