DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing; WO 51 / Room 2269 10903 New Hampshire Avenue Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	02/27/2023-03/10/2023
	FEI NUMBER 3012163998

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Yeongman Yoo, Plant Manager

FIRM NAME	STREET ADDRESS
Hugel, Inc. (Site 2)	23 Geodudanji1-gil, Dongnae-myeon
CITY, STATE, ZIP CODE, COUNTRY Chuncheon-si, Gangwon-do, 24398, Republic of Korea	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Your firm lacks an established cleaning and disinfection program to prevent the introduction of microbial contamination, including *Clostridium botulinum* spores and toxin, into controlled manufacturing environments in your Building (b) (4) drug substance and drug product manufacturing facilities.

Specifically,

A. You failed to conduct a study to demonstrate that the effectiveness of cleaning/sanitizing agents for the removal of Botulinum Neurotoxin A (BoNT/A) residue from the manufacturing surfaces in the facilities.

B. Your disinfectant efficacy study, ALC21017-R-00 (approved 2021-11-24), does not adequately support the effectiveness of (b) (4) disinfectants for the removal of *Clostridium botulinum* from all representative manufacturing surfaces in the facilities. For example, materials of contact (MOC) for (b) (4) and wall/ceiling finishing (b) (4) were not included in the study. In addition, the study failed to include sufficient evidence to demonstrate the *Clostridium botulinum* spore log reduction achieved on the tested surfaces using the disinfectants.

C. You failed to ensure sufficient use of a sporicidal agent in your disinfection program. For example, a sporicidal agent is not used to perform periodic cleaning and disinfection of all Grade C and Grade D manufacturing areas in the facilities.

D. Your disinfectant efficacy studies, ALC19001-R (approved 2019-03-19), ALC19011-R (approved 2019-09-10), ALC20015-R (2020-12-10), and ALC22007-R-01 (2023-03-02), do not adequately support the sanitization procedures for the antimicrobial and sporicidal effectiveness of the disinfectants and sporicidal agents for all representative manufacturing surfaces in the facilities. For example, MOCs for (b) (4) (b) (4) wall/ceiling finishing (b) (4) and filling-line conveyor belts were not included in the studies. In addition, only the vegetative form of spore-forming (b) (4) ATCC (b) (4) was used in the studies.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Zhong Li, Senior Pharmaceutical Quality Assessor Yetao Jin, Chemist	03/10/2023

E. Your cleaning and sanitization procedure for the classified manufacturing areas, AWLS-FE-008-20 (version 20, effective 2023-02-24), does not require documentation and verification that the surfaces are (b) (4) and remain (b) (4) for the contact time validated in the disinfectant efficacy studies.

OBSERVATION 2

Laboratory records are deficient in that your firm has not established adequate procedural controls to ensure assay data traceability, reliability, and accuracy.

Specifically,

A. Regarding the (b) (4) Assay for BoNT/A DP potency, the following were noted during the inspection:

1. Uncontrolled forms were used to record raw data. Specifically, loose paper was used for "Test Record of (b) (4) Injection (Potency) (b) (4) Lot No HUB23031 from February 27, 2023 to March 2, 2023. Your Quality Unit failed to establish adequate document control of the forms that are used for GMP activities.

2. Contemporaneous verification during laboratory tests is inadequate. For the potency assays for DP lot HUC 23033 and DP lot HGB23027, the animal injections by (2) analysts were conducted in the same room (b) (4) at almost the same time on February 27, 2023. The two analysts did not crosscheck each other's samples and animals during and after the injections. During the observation at (b) (4) for the potency assay of DP Lot No HUB23031 on February 28, 2023, the crosscheck between the analyst and the observer was not observed.

3. There was no tractable evidence for dead and alive (b) (4) for the post-injection observation in the potency assays. The analyst and the observer only recorded the numbers of dead animals in each cage on the loose forms during the observations at (b) (4) There was no evidence to trace back and verify dead and alive animals in each cage at each observation timepoint.

4. There was no reconciliation for dead and alive animals at disposal. After the final observation at (b) (4) (b) (4) for the potency assay of DP Lot No HUB23031, the animal cages were transferred from the observation room (b) (4) to the euthanasia and waste disposal room (b) (4) The numbers of dead and alive animals were not verified. The alive animals were separated and sacrificed in a (b) (4) chamber prior to disposal. The dead animals were disposed directly.

B. Regarding the Neurotoxin content ELISA assay for BoNT/A DP, the following were noted during the

inspection:

1. The "Neurotoxin content" section of the test record does not include plate layout to indicate sample locations on a plate for a specific test. The locations of samples were not documented at the plate setup.

2. There was no contemporaneous verification to ensure that the samples were added on the plate correctly in the neurotoxin content test for the (b) (4) accelerated stability sample (b) (4) under 25°C±2°C/RH 60%).

OBSERVATION 3

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

Specifically,

A. While observing the aseptic setup and filling operations for the filling of BoNT/A drug product on 28 February 2023 and 06 March 2023, the following deficiencies were noted:

1. Operators were observed extending (b) (4) over the sterile components (*e.g.*, unfilled, (b) (4) vials) and violated first air principles while performing interventions inside the filling line.

2. While installing the (b) (4) the operators were observed placing his/her gloved right hands over the exposed direct product-contact surfaces of the (b) (4) In addition, operators were observed touching the unprotected (b) (4) of the (b) (4) with his/her gloved hands, while attempting to connect the (b) (4) tubing to the (b) (4)

3. While installing the (b) (4) operators blocked the first air over the unprotected (b) (4) with the (b) (4) In addition, an operator was observed touching a (b) (4) with the exterior of the (b) (4) protection bag.

4. While installing the (b) (4) the operator was observed holding the unprotected sterile (b) (4) with his/her gloved hands.

5. While installing the (b) (4) operators blocked the first air over the exposed indirect product-contact surfaces of the (b) (4) with (b) (4) while removing the

(b) (4)

6. RABS (b) (4) by the (b) (4) and (b) (4) were opened and closed multiple times during the aseptic setups without wiping down the inside surfaces of the RABS including the (b) (4) The primary setup operators' gloved hands were not sanitized during the set-up operations.

B. Environmental and personnel monitoring of aseptic processing areas following aseptic assembly of filling components and aseptic filling operations are deficient. For example,

1. Surface or settle plate anaerobic environmental monitoring is not conducted to ensure that the drug product manufacturing areas are not contaminated with *Clostridium botulinum*. Only anaerobic airborne viable monitoring is conducted during the filling operations.

2. During the routine environmental monitoring following the filling activities, not all sanitized or non-sterile equipment surfaces above the sterile filling and stoppering components (direct and indirect product-contact) on the filling line were adequately sampled. For example, microbiological surface samples were not taken from the (b) (4) stoppering station, (b) (4) bracket, and (b) (4)

3. During the routine environmental monitoring following the aseptic set-up activities, personnel contact-plate samples were only taken from the primary operators' fingers (finger dab). The operators placed their head and upper torso inside of the Grade A RABS to perform the set-up activities. In addition, the goggles used by the operators have open vents on the top of the goggles.

4. During the aseptic assembly and filling operations, RABS (b) (4) were used (b) (4) (b) (4). These RABS (b) (4) are not required to be monitored (b) (4) during environmental monitoring following filling activities. Monitoring of the (b) (4) should be performed according to their use.

5. Environmental monitoring in the aseptic filling line is not appropriately positioned in locations to optimize detection of environmental contaminants. For example,

   i. There is no viable air monitoring or settling plate in the immediate vicinity where open vials are located on the (b) (4) after depyrogenation and in the vicinity where interventions are conducted by operators inside the RABS to remove fallen vials from the (b) (4)

   ii. Viable air monitoring is not conducted where (b) (4) vials travel from (b) (4)

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing; WO 51 / Room 2269 10903 New Hampshire Avenue Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	02/27/2023-03/10/2023
	FEI NUMBER 3012163998

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mr. Yeongman Yoo, Plant Manager	
FIRM NAME Hugel, Inc. (Site 2)	STREET ADDRESS 23 Geodudanji1-gil, Dongnae-myeon
CITY, STATE, ZIP CODE, COUNTRY Chuncheon-si, Gangwon-do, 24398, Republic of Korea	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product Manufacturer

to the point of being loaded to an (b) (4) for (b) (4) which is a distance of approximately (b) (4).

6. Appropriate alert or action limits have not been established for fungal contamination in the Grade C and Grade D areas. Only a cumulative account of bacterial and fungal colonies is evaluated against the alert/action limits for the classified areas. Consequently, your environmental monitoring program lacks assurance of a timely and sensitive detection of adverse trend of fungal contamination in your facilities. There were (17) mold recoveries that were reported in the Grade B areas in 2022.

OBSERVATION 4

Your environmental monitoring program for the Building (b) (4) drug substance manufacturing facility is deficient.

Specifically,

You failed to conduct environmental monitoring that is specific for the spore-former, *Clostridium botulinum*, in the classified drug substance manufacturing areas.

OBSERVATION 5

Your firm's quality unit's oversight of your GMP manufacturing operations is inadequate.

Specifically,

A. Your firm has not established adequate procedural controls to protect the electronic data acquisition systems. For example,

1. The Validator-1 (QV-VAL01) and Validator-3 (QV-VAL03) systems installed on a LENOVO laptop (S/N PF34YNJ0) have not been validated. The systems are used to collect data from dataloggers during the temperature mapping and thermal validation of critical process equipment, including (b) (4) validation and (b) (4) validation.

2. Deviation #DV22-014 (dated March 08, 2022) documents a software bug found on the EndoScan-V Endotoxin Testing System (version 5.5.3), which allows the user to overwrite the existing data. This software system is used to collect endotoxin data from a microplate reader (equipment # LM-MPR04) in the QC microbiology laboratory. An appropriate action has not been taken to resolve the software issue to prevent the unexpected or unauthorized modifications to stored testing data.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing; WO 51 / Room 2269 10903 New Hampshire Avenue Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	02/27/2023-03/10/2023
	FEI NUMBER 3012163998

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Mr. Yeongman Yoo, Plant Manager	
FIRM NAME Hugel, Inc. (Site 2)	STREET ADDRESS 23 Geodudanji1-gil, Dongnae-myeon
CITY, STATE, ZIP CODE, COUNTRY Chuncheon-si, Gangwon-do, 24398, Republic of Korea	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product Manufacturer

B. There is a lack of assurance that your cleaning procedures, used for product-contact process equipment used to manufacture the BoNT/A products, are effective in preventing cross-contamination. For example,

1. During the walkthrough inspection of FD Technical Zone (Room (b) (4) on February 27, 2023, we observed residues on the inside of viewport windows (sight glasses) of the freeze dryers (MP-FD01 and MP-FD02) that were cleaned and ready for use.

2. Cleaning validation (CV) study, AHGCVP22001-10 (approved 2022-12-19), failed to include swab samples from process equipment including: Fementor-1, the (b) (4) and freeze-dryers.

C. There is a lack of scientifically sound justification for the size of the in-process control samples taken during the DP manufacturing. Specifically, (b) (4) samples are taken for each filling operation on the filling line with (b) (4) for a batch of (b) (4) vials.

D. Testing of critical materials is not adequate. Specifically, bioindicators, used for equipment sterilization validation, are not tested for viable spore counts before use, nor are analyses conducted to verify the reliability of the supplier's certificates of analysis for (b) (4)

E. Shipping validations for samples that are tested in your contractor testing laboratories have not been conducted.

F. Your firm has not adequately qualified the critical utility used for the drug product manufacturing processes. Specifically, the (b) (4) delivered to the facility has not been sampled at the points of use and tested for purity and impurities as specified in the USP-NF.

3/10/2023

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	YJ	Zhong Li, Senior Pharmaceutical Quality Assessor Yetao Jin, Chemist	03/10/2023