DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Mahesh Ramanadham, Acting Division Director CDER/OPQ/OPF WO Bldg 51, Room 4238 10903 New Hampshire Ave, Silver Spring, MD 20993 Phone: 301-796-1272 Industry Information: www.fda.gov/oc/industry	11/08/17-11/17/17
	FEI NUMBER 3012333115

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Kim Jun, Head of Nabota Quality

FIRM NAME	STREET ADDRESS
Daewoong Pharmaceutical Co., Ltd.	35-14, Jeyakgongdan 4-Gil, Hyangnam-Eup
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Hwaseong-Si, Gyeonggi-Do Republic of Korea 18623	Drug Substance and Sterile Drug Product 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 and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

1. No investigation has been conducted to determine the source of particles and the recurrence of this issue. For example, during the 100% visual inspection of process validation drug product (b) (4) batches manufactured in Building (b) (4), (b) (4) black particles were found and the acceptance criteria was exceeded. Although the acceptance quality limits (AQL) test was subsequently performed and it passed, there is no documentation to support the size of the particles identified in order for these to be classified per levels as major, intermediate and minor per standard operating procedure, NPR03-066: Qualification of visual inspection, and pass the visual inspections. In addition, black particles were also observed in development batches of (b) (4) manufactured in Building (b) (4), (b) (4) with rates as high as (b) (4) % and (b) (4) %.

2. Deviation #17017 related to the assignment of an incorrect lot number determined that the person in charge assigned the incorrect lot number. A CAPA (NCP 17023) was initiated to create a form to avoid this error in the future; however, the CAPA was later canceled noting that this issue would better be handled during (b) (4) management meetings. There was no retraining or preventive measures taken to mitigate this problem.

3. Temperature distribution tests (three runs) for the anaerobic chamber failed to meet performance qualification criteria during (b) (4) requalification period. The failure to maintain an even distribution of temperature was attributed to the aging of the equipment. The corrective action was to have operators work in a designated marked area within the chamber, which is used for thawing the WCBs (temperature specified as (b) (4) ° C +/- (b) (4) ° C) and for seed preparation and culture. (b) (4) batches of DS have been manufactured and placed in the

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inadequately qualified instrument.

OBSERVATION 2

All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure the drug substance conforms to its established standards of quality and/or purity.

Specifically,

1. The standard operating procedure NQC01-006, Establishment and Control of Reference Standard and Critical Reagent, does not specify the need for verification of the specificity of the antibodies for its intended use. The critical reagent, (b) (4) antibody used for drug substance identity testing by Western Blot was not verified for its specificity to demonstrate that the antibody only recognizes (b) (4) and does not cross-react with other serotypes. The drug substance identity is one of the critical product quality attributes tested at release.

2. The endotoxin method verification for the drug substance is inadequate in that your firm failed to use the actual drug substance to ensure the method is reliable and suitable for its intended use.

OBSERVATION 3

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

Specifically,

There is no documentation to ensure that environmental monitoring (EM) samples are traceable and attributable. For example, the collection of EM samples is not recorded at the time of collection. We observed notes (raw data) regarding EM samples (ex. Settle plates times) recorded on erasable laminated worksheets during the production run for lot (b) (4); however, this data is not retained.

Additionally, EM samples are not handled in the same manner as other samples in the QC laboratory. For example, these samples are not tracked through the sample intake methods used for other types of samples.

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OBSERVATION 4

There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures: Aseptic processing, which includes as appropriate: A system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

1. NPE05-046: Operation and Maintenance of (b) (4) (Equip No: (b) (4) 01) (Building (b) (4), approved 10/31/17, requires closing the (b) (4) conveyer and (b) (4) conveyer areas with masking tape. Surface area inside the ISO 5 area covered with this masking tape is not fully exposed to the (b) (4) and any residue left from application of the masking tape is not assessed.

2. NP503-006: Operation and Maintenance of (b) (4) Disinfectants, approved 09/15/17, establishes a contact time of ≥ (b) (4) for (b) (4); nonetheless, the PV-R-15085: Disinfectant Efficacy Validation Report, approved 05/11/16, establishes the minimum contact time for (b) (4) as (b) (4) in the (b) (4) surface (RABS) for it to be effective.

OBSERVATION 5

Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

Specifically,

Airflow pattern testing approved 10/5/16 does not demonstrate unidirectional airflow. These tests were conducted utilizing (b) (4) per NPE07-006: Air Flow Visualization Test, which dissipates rapidly when generated from the source. The air flow pattern at the operation level cannot be effectively visualized.

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Additionally, NPE07-006: Air Flow Visualization Test, approved 10/05/16, does not delineate the requirement to conduct dynamic air flow pattern studies to simulate operations or interventions in the production area.

OBSERVATION 6

Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

Specifically,

1. Monitoring in the Grade A (b) (4) used in the (b) (4) stages of the drug substance manufacturing, including sterile (b) (4) of the DS, is inadequate to ensure that Grade A conditions are met during operations. Limited testing is performed during production. The only EM samples collected are viable air samples are collected from (b) (4) prior to production operations and operator samples (fingertips only) are collected after the operation is completed. However, no particulate monitoring, settle plates or contact plates are sampled during production in the (b) (4) There is a higher risk of contamination of the DS due to the exposure of the product during this stage of the process.

2. There are no cleaning validation studies for the (b) (4) to ensure that impurities from the (b) (4) purification in the DS manufacturing process do not contaminate the downstream material during the (b) (4) purification using the same (b) (4)

3. There is no justification for the (b) (4) filter integrity testing frequency for the (b) (4) filter used to supply (b) (4) to the anaerobic chamber. This filter is critical to mitigate the risks of contamination of the (b) (4) seed cultures during the (b) (4) stages of the drug substance manufacturing.

OBSERVATION 7

Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written

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procedures shall be recorded and justified.

Specifically,

The written procedure for Assigning Batch Number and Date of Manufacture (NDC01-005) lacks specific instructions for assigning batch number for drug product (b) (4) This has resulted in several deviations related to batch assignment numbers such as: (b) (4)

OBSERVATION 8

Appropriate controls should be exercised over computer systems to assure that changes to records are instituted only by authorized personnel.

Specifically,

Computer system validation for the WinKQCL software (endotoxin testing) is deficient in that the functionality testing related to user access and data security did not include challenges to demonstrate that data cannot be altered, manipulated or deleted.

OBSERVATION 9

Materials should be handled and stored in a manner to prevent degradation, contamination and cross-contamination.

Specifically,

Your firm failed to consistently use the SAP system for material inventory and location. For example, the master and working cell banks for (b) (4) were moved from Building (b) (4) freezers to the Building (b) (4) freezers due to an unexpected fire (in Building (b) (4) ; however, the movement of these cell banks was not documented in the SAP system.

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OBSERVATION 10

Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

Specifically,

There is no established standard operating procedure delineating training for contractors with access to computerized systems such as Building Management System.

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