DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Baltimore District Office # 410-779-5454 6000 Metro Drive; Suite 101 Baltimore, MD 21215 Industry Information: www.fda.gov/oc/industry	5/19, 20, 21, 26, and 29/2015
	FEI NUMBER 3011547221

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Robert (NMI) DeChristoforo, Chief Pharmacy Department

FIRM NAME	STREET ADDRESS
NIH - Clinical Center Pharmacy	10 Center Drive; Building 10; Room 4436
CITY, STATE AND ZIP CODE Bethesda, MD 20892	TYPE OF ESTABLISHMENT INSPECTED Hospital Pharmacy

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 (I) (WE) OBSERVED:

1) Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, an operator was observed processing sterile drug products with an exposed wrist from a gap between their gloves and their gown. The same operator had exposed facial hair.

2) Systems for maintaining equipment used to control aseptic conditions in the aseptic processing areas are deficient.

Specifically, there are no air flow pattern studies performed in the ISO 5 horizontal airflow hood used to prepare total parenteral nutritional drug products and no dynamic airflow pattern studies were performed to determine whether products are protected from non-sterility risks in any of the five ISO 5 hoods used to make other drug products intended to be sterile.

3) The system for cleaning and disinfecting the room and equipment in the aseptic processing areas to produce aseptic conditions are deficient

Specifically, the cleaning and disinfection program for the ISO 7 and ISO 5 areas does not include a sporicidal disinfection agent.

4) Drug product operations and procedures are not performed in specifically defined areas of adequate size to prevent contamination or mixups.

Specifically, facilities were not designed and controlled to prevent contamination risks to sterile drugs in that:
a) There is inadequate separation of the aseptic processing area from the common pharmacy and uncontrolled flow

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
		Ernest F. Bizjak, Compliance Officer Thomas J. Arista, Investigator Brooke K. Higgins, Consumer Safety Officer Tamara Ely, Consumer Safety Officer	5/29/2015

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of personnel between the two areas.

b) There is a lack of a differential pressure cascade between adjacent areas. The Deputy Chief Pharmacy Department explained "that no air pressure differential measurements" can be obtained "in the pharmacy because there are no doors" i.e., between the compounding area and the adjacent pharmacy preparation area. There is no specific minimal airflow velocity from the buffer area to the adjacent pharmacy as the feet per second air velocity is unknown.

c) Chemotherapeutic drugs are produced in an area that is not negatively pressured for containment.

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1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

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TO: Mr. Robert (NMI) DeChristoforo, Chief Pharmacy Department

FIRM NAME	STREET ADDRESS
NIH - Pharmaceutical Development Section	Building 10 Room 1c240; 10 Center Drive
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Bethesda, MD 20892-0001	Clinical Supply Manufacturing Facility

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:

The following observations are for the NIH - Clinical Center Pharmacy Department Pharmaceutical Development Section:

FACILITIES AND EQUIPMENT

OBSERVATION 1

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically, the air system was not adequately designed and controlled to assure appropriate air quality in the room in which aseptic processing is performed. The positive pressure was not consistently maintained between the ISO 7 aseptic processing cleanroom and areas of lower quality air (e.g., gowning room, clean prep room, and common hallway). Monitoring data showed that the aseptic processing cleanroom pressure was negative to the gowning room during the May 19, 2015 filling of Copper Histidinate Injection lot 139623.

Furthermore, air pressure differentials for the classified areas are monitored via the Rees Environmental Monitoring computer based system. However, the data are not routinely reviewed to assess batch impact.

OBSERVATION 2

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically, an exhaust vent, approximately one foot in diameter, is located in the ceiling above the autoclave exit door in the ISO 7 cleanroom where the ISO 5 horizontal air flow hood is located. The exhaust vent runs from the ISO 7 cleanroom to

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the roof of the facility, fourteen (14) floors above. There is no filter or screen covering the vent opening into the ISO 7 cleanroom. Sterilized supplies for aseptic processing are discharged from the autoclave directly underneath this exhaust vent.

OBSERVATION 3

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

Specifically,

a. There was a lack of information about the microbial quality of the environment in which aseptic processing is performed. For example:
   i. There is no monitoring of the air for microorganisms during aseptic filling operations.
   ii. Microbiological sampling of personnel and the ISO 5 horizontal airflow hood surfaces are not routinely performed during each production run. For example, personnel sampling and surface sampling was performed during the aseptic filling of only 27 drug products out of approximately 73 aseptically filled since October 30, 2014.

b. Particle levels were not adequately monitored or well-controlled in the ISO 5 zone in which sterile drug components are exposed during processing. For example:
   i. The level of particles present during aseptic processing was not measured between January 6, 2015 and February 26, 2015. There was no measurement of non-viable particulates in the ISO 5 horizontal airflow hood during this time. There were at least twenty-two (22) sterile drug products made in the ISO 5 horizontal airflow hood during this timeframe.
   ii. The two probes used to measure total non-viable particulates in the ISO 5 horizontal airflow hood are not placed in close proximity to aseptic manipulations. Instead, both probes were observed to be placed immediately in front of the HEPA filter face.
   iii. The limit for ISO 5 locations is 100 particles per cubic foot. Non-viable particulate readings at the HEPA filter face periodically reached or exceeded the limit of detection of 1000 particles per cubic foot. For instance, during the May 19, 2015 filling of Copper Histidinate Injection lot 139623, non-viable particulate readings reached the limit of detection on three (3) separate occasions.
   iv. The non-viable particulate system alarms were inhibited in the Rees System at the time of the inspection. Personnel performing aseptic filling of drug products would not be aware if the non-viable particulate counts were unacceptable.

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OBSERVATION 4

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically, the ISO 5 horizontal airflow hood used for aseptic processing was not demonstrated to be capable of protecting the exposed sterile drug from microbial contamination during processing. Air flow pattern studies for the ISO 5 horizontal airflow hood did not demonstrate that it produces unidirectional airflow during production conditions. The studies conducted in 2010 were of short duration and did not include dynamic operations or configuration of equipment consistent with normal operations.

OBSERVATION 5

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

Specifically,

a) The cleaning and disinfection program for the ISO 5 hoods (horizontal airflow hood and the biological safety cabinet) does not include the use of a sporicidal agent to prevent non-sterility hazards from spore forming microbes (e.g., certain bacteria and fungi) in the environment. Spore-forming organisms such as Cladosporium and *Aspergillus midulans* were found in two released vials of Albumin Human Serum 5% injection lot 138417, and Bacillus species and Hyaline Septate mold were isolated from the environment.
b) No sterilization cycle is performed to ensure the lyophilizer is free of microorganisms prior to use. The lyophilizer is only disinfected with IPA.
c) Cleaning of the ISO 5 horizontal airflow hood is not always documented.
d) One package of wipes released for use to clean and disinfect the ISO 5 hoods was observed to have a hair like particle visible within the intact package.

OBSERVATION 6

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

Specifically, insects were observed in two (2) of the five (5) ISO 7 cleanroom ceiling light bays on May 20, 2015 and there were visible gaps in the caulking around each light bay.

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QUALITY

OBSERVATION 7

The accuracy, sensitivity, and specificity of test methods have not been established.

Specifically, the BACTEC system used for sterility release testing is not validated and has not been shown to be equivalent to USP <71>. The BACTEC system was used to release Albumin Human Serium 5% injection lot 138417.

OBSERVATION 8

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

Specifically, investigations into non-sterility, or potential sterility hazards, are not appropriately conducted. For example:

a. The investigation into the sterility failure of GVHD ASED lot 137541 did not establish a root cause. A "Formulator" confirmed that they did not identify any actions to be taken to prevent a recurrence.
b. Lidocaine Hydrochloride Buffered lot 138204 was documented to have had a "false positive" result for sterility testing by the in-house BACTEC method. No organisms were seen by Gram stain or on bacterial fluorescent stain from the original sample. A "Formulator" confirmed that there was no sterility retest performed and the lot was released.
c. Investigations are not always conducted to evaluate the impact of positive environmental and personnel samples collected from the ISO 5 area, or adverse trends. For example, investigations did not adequately evaluate the following positive samples:
    i. Thirteen (13) personnel monitoring samples and two (2) surface samples collected since October 30, 2014 were found to have positive growth.
    ii. A gram negative organism (*Moraxella osloensis*) was identified on a sample collected from the left forearm of "Formulator" LF.
    iii. Eight (8) of the thirteen (13) positive personnel samples obtained since October 30, 2014 were collected from "Formulator" LF.
d. Three (3) vials were removed from Sodium Phosphates Injection lot 135838 during the 100% post-fill inspection prior to release for contamination with glass particles. A "Formulator" confirmed that there was no root cause identified, and no preventive actions initiated to prevent a recurrence.

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OBSERVATION 9

The quality control unit lacks the responsibility and authority to approve and reject all components, drug product containers, closures, and drug products.

Specifically, the quality unit is not responsible for the approval or rejection of all components, drug product containers, closures, and drug products. For example,

a. The quality unit is not involved in release of drug products to ensure appropriate identity, strength, quality, and purity.
b. The quality unit is not immediately notified of deviations that occurred during the production or testing of drug products.
c. The quality unit does not review autoclave, vial washer, or depyrogenation oven cycles to ensure the cycles were appropriately completed.
d. The quality unit does not review environmental conditions, such as differential pressure, non-viable particulates, and HEPA filter recertification to ensure that sterile drugs were produced under environmental conditions that are suitable for aseptic processing.
e. The quality unit does not confirm formulation records adhere to the Investigational New Drug (IND) application.

OBSERVATION 10

Determinations of conformance to appropriate written specifications for acceptance are deficient for drug products.

Specifically, there was inadequate visual inspection of sterile products to ensure they are free of visible contamination. A released vial of Potassium Chloride Injection lot 131558, expiration date July 31, 2015, that had passed visual inspection on August 2, 2012 was observed on May 19, 2015 to contain a single, floating black particle

OBSERVATION 11

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, "Formulators" aseptically filling sterile drug product on May 19, 2015 were observed to have gowning that failed to fully cover their face and neck area.

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OBSERVATION 12

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically, the stability program does not routinely evaluate product sterility over the product's shelf-life. Shelf life was observed up to three years. For example, Potassium Chloride Injection lot 131558 was observed to have a three year expiry. In addition it was observed that expiration dates were applied to biologic products, such as Albumin Human Serum 5% lot 138417, for up to three years. Biologic products provide a rich media for growth and are susceptible to microbial contamination.

OBSERVATION 13

GMP training is not conducted on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

Specifically, training is not appropriately conducted. For example:

a) There is no GMP training program; a "Formulator" explained that he has not received GMP training.
a) New contract cleaning personnel clean and disinfect the facility, including the ISO7 cleanroom, without receiving any training on the facility cleaning and disinfection procedure.

PRODUCTION

OBSERVATION 14

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

Specifically, the following sterility assurance deficiencies were observed:

a) Partially stoppered vials are not protected or maintained under ISO 5 conditions as they are manually transferred through the ISO 7 cleanroom to the lyophilizer. For example, this contamination hazard to unsealed product was observed on May 19, 2015 during transport of partially stoppered vials of Copper Histidinate Injection lot 139623.
b) Filter integrity testing is not routinely performed following the sterilization of drug products. Since installation of the test equipment in May 2014, there is evidence to show that filter integrity testing has occurred only once.
c) There are no media fill simulations to qualify the aseptic process and formulators.

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d) The facility, including the cleanroom, experiences a monthly power failure when the hospital verifies the emergency/back-up power system works. There are no procedures established, nor any cleaning and disinfection performed, to prepare the area to resume processing after a power failure.

e) The following aseptic behaviors were observed during aseptic filling operations of Copper Histidinate Injection lot 139623 on May 19, 2015:
   i. A "Formulator" was observed touching a chair in the ISO 7 cleanroom with their elbow and then resting the same elbow on the work surface of the ISO 5 horizontal airflow hood. The chair was not observed being routinely disinfected.
   ii. "Formulators" rested their hands and forearms on the work surface of the ISO 5 horizontal air flow hood.
   iii. "Formulators" infrequently sanitized their hands during aseptic filling operations and on re-entry into the ISO 5 horizontal air flow hood

f) Sterilized filling equipment, such as tubing, is not assigned an expiration date at which point it must be resterilized. For instance, sterilized tubing autoclaved on November 4, 2014 was observed on May 21, 2015 available for use in a storage cart in the ISO 7 cleanroom. "Formulator" LH stated that equipment can be held approximately four to five months before it must be resterilized

OBSERVATION 15

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

Specifically, load patterns and process cycles have not been developed and validated to ensure the adequacy of washing, sterilization and depyrogenation cycles used to process containers, closures and equipment.

Furthermore, there is no evidence to show that vial washer, autoclave, and oven cycles are reviewed to ensure they have been appropriately completed for each batch.

MATERIALS

OBSERVATION 16

Each lot of a component liable to objectionable microbiological contamination is deficiently subjected to microbiological tests before use.

Specifically, there is a lack of assurance that the system producing water used to formulate sterile drug products and clean

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equipment used to manufacture sterile drug products is appropriately designed and controlled. For example:

a) The water produced on site was tested only twice in 2014 (April 3 and 18, 2014) and twice in 2015 (March 31 and May 6, 2015) for endotoxin and is not monitored for microbial growth.

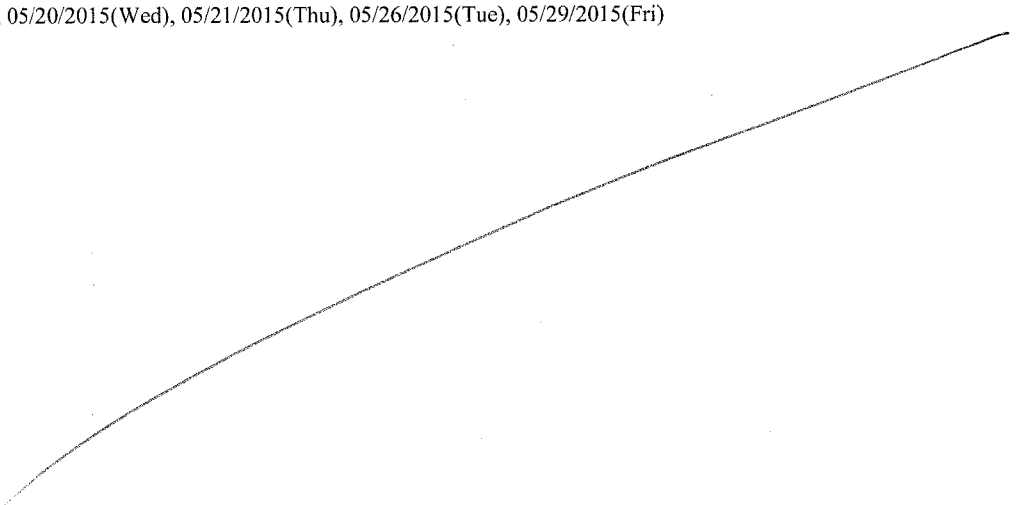
b) The system design was inadequate. For example, there is an approximately ten (10) inch long by two (2) inch diameter stainless steel pipe at the bottom of the 100 gallon stainless steel purified water condensate storage tank. The Chief of PDS confirmed that it is a "dead leg", which could be a reservoir for stagnant water and microbial proliferation.

OBSERVATION 17

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Specifically, container closure integrity testing is not performed for any sterile drug products.

*** DATES OF INSPECTION:**
05/19/2015(Tue), 05/20/2015(Wed), 05/21/2015(Thu), 05/26/2015(Tue), 05/29/2015(Fri)



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