NIH Interim Corrective Action Plan in
Response to Inspectional Observations of the
NIH Clinical Center Pharmaceutical Development Section Dated June 2, 2015

NIH thanks the FDA investigators for their thoughtful observations during the inspection of its Pharmaceutical Development Section (PDS) that concluded on 5/29/15. NIH takes these observations very seriously and our senior leadership is committed to take all the necessary measures to ensure our research participants' safety and correct all deficiencies. Effective 5/22/15, the Clinical Center decided to place a hold on production in the PDS sterile products area. Also, the Clinical Center quarantined all sterile products in the current inventory that had been produced prior to 5/22/15. PDS has also implemented re-testing of all quarantined lots, using visual inspection, pyrogen testing, and USP sterility testing. The Clinical Center will not resume sterile products production until all observations are addressed and the facility is inspected by an independent organization to establish that the PDS can meet current Good Manufacturing Practices (cGMP) standards and FDA agrees that production should resume.

NIH has provided responses to each observation in the Form 483 report. NIH responses to each observation address each concern, on both individual and systemic bases.

The observations have identified several systemic issues that can be categorized into three areas: 1) facility evaluation and improvement; 2) personnel training and competency maintenance; and 3) development and maintenance of appropriate SOPs for all activities. The NIH will retain a highly respected consulting firm that is qualified, knowledgeable, and experienced in the application and implementation of cGMP activities that are necessary to support manufacturing of sterile pharmaceutical products. In order to take full advantage of that expert advice, NIH will limit internal review of the PDS to assessment of the deficiencies outlined in the FDA 483 forms, but will not seek to remediate those until the consulting firm has provided recommendations. The consulting firm will complete full evaluations of the PDS facility, its operations, its procedures and processes, and its quality assurance and quality control system and will make recommendations for improvement. The firm will also assist NIH in the development of a corrective action plan to address specific FDA concerns that will help us assure compliance with cGMP regulatory requirements for the foreseeable future. Once the inspections are completed NIH will ask the FDA to register the PDS as a cGMP manufacturing facility, and will make plans for periodic announced and unannounced routine inspections by qualified experts. In addition, NIH plans to establish a senior advisory committee consisting of experts in GMP-facility management, clinical research, engineering, and regulatory requirements to oversee the entire process and receive reports from the GMP contractor.

To that end, the immediate milestones are:

- Retain a GMP consulting firm by 6/24/15
- Develop corrective action plan by 8/14/15 (*Estimated, will be dependent on consulting firm deliverable)*

- Train/Re-train personnel with GMP-specific training courses by 8/14/15
- Develop all necessary Standard Operating Procedures (SOPs) by 9/1/15

Additionally, NIH has developed a draft plan with priorities and timelines for its next set of actions. Once approved by FDA, NIH leadership will closely monitor the implementation of this plan and will provide FDA with updates on NIH progress on a monthly basis, including evidence of ongoing implementation. NIH leadership will also directly monitor the effectiveness of its corrective action plan on a long-term basis.

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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.

Response to Observation 1: NIH believes that correcting and maintaining control of the air supply is a critical issue and will be a priority for remediation.

The PDS's current system includes a Siemens monitoring system connected to the main facility air handling systems and a REES monitoring system in the sterile products area. NIH has already had several meetings and walk-throughs with the NIH Office of Research Facilities (ORF) staff to conduct a thorough facilities review, to make initial observations, and collect baseline data. These concurrent ongoing activities include:

- assuring the integrity of the design as appropriate to support sterile manufacturing;
- comparing the facility compliance data, design data, and air quality data to ensure that the as-designed drawings and specifications meet performance characteristics;
- compiling and analyzing data collected by the Siemens system to assess how the system is functioning and to look for trends;
- ensuring that the REES system is installed appropriately to meet it's intended purpose of accurately monitoring of the differential pressures;
- correlating Siemens differential pressure data with the REES system;
- examining redundancies in the system and effect of the transition between systems.

NIH will provide these baseline and historical data to the cGMP consulting firm, to facilitate both their evaluation and to develop an interim corrective action plan by 8/14/15 (*estimated, pending consulting firm contract).* The plan will include an evaluation of the current PDS system to monitor differential pressures.

Along with correcting the airflow issues, NIH will develop policies based on the consultant's recommendations as soon as possible to require review and documentation of the airflow conditions before, during, and after production of a batch of medication and also during times when the sterile room is not used.

Additionally a policy will be created by 9/1/15 that addresses actions that are required to be taken when differential pressures are detected as being out of range before allowing the sterile processing unit to resume production in the sterile production area.

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 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.

Response to Observation 2:

The need and purpose of the exhaust vent has already been discussed with NIH facility personnel. The correction of this issue (e.g., cover, block, or remove the vent) will be included in the consulting firm's assessment and recommendations, as will techniques for optimally maintaining proper air flow and differential pressures in the affected room. The corrective action plan will be developed as soon as is possible following receipt of the consultant's report.

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.

Response to Observation 3:

3a.i & ii - NIH will actively monitor the environment with settling plates. NIH also will monitor the environment with MiniCapt active air samplers that allow for remote sampling. These devices will be calibrated and readied for use by 7/1/15.

By 9/1/15, NIH will create an SOP for this procedure, train personnel in proper use, and assess their competencies. Documentation will be included in batch production logs for the results of the sampling during batch production. Competencies will be assessed every six months by the Chief, Pharmacy Department and will be reviewed by the Clinical Center Deputy Director for Clinical Care.

PDS will establish an SOP for microbial sampling by 9/1/15 and will implement sampling for each batch when operations resume. NIH will train an adequate number of personnel prior to resuming operation to ensure these monitoring procedures are used in every production batch.

3. b.i-iv – The remediation for these observations depends on several factors. NIH is asking the consulting firm to conduct a thorough gap analysis for these issues, including providing NIH with recommendations for correcting the airflow issues, for re-evaluating how NIH monitors particulates throughout the area, for developing and implementing an improved process to alert personnel operating in the room that particulates are out of range, and for documenting the particulate monitoring data during production of each individual product.

NIH will work with the consulting firm, with the expanded cGMP QA Team, and with NIH facility personnel to incorporate these considerations when the facility is evaluated. NIH will implement the proper system for monitoring as part of the facility evaluation/remediation

plan (8/14/15, *Estimated, pending consulting firm contract)* and develop the appropriate SOPs for sampling and reporting (9/1/15).

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

Response to Observation 4:

NIH's has an ongoing contract with a company that evaluates air handling in several of its facilities. This current contractor will conduct, both the static and dynamic smoke studies for horizontal flow hoods and biologic safety cabinets. NIH will extend this contract to include dynamic smoke studies for all hoods and all operators in the sterile processing area of PDS. These studies will be conducted with every individual producing sterile products. Studies for each operator will be conducted and videotaped every six months.

An SOP will be developed by 9/1/15 for the smoke study process, frequency, and documentation.

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.

Response 5:

5a and c – The Clinical Center has consulted with its hospital safety officer and has identified

an effective, EPA Registered, sterile sporicide, virucide, tuberculocide, bactericide and fungicide (Steriplex SD) as a disinfecting agent. Working with the consulting firm, NIH will create a written SOP by 9/1/15 to address proper use and protection when using a sporicidal agent, proper hood cleaning, and documentation procedures.

5b – NIH will also ask the cGMP consulting firm to recommend methods to provide proper sterilization for the existing lyophilizer that is consistent with FDA guidance. Based on input from the consultant, if the existing lyophilizer cannot meet these requirements, the Clinical Center will either purchase a new lyophilizer or re-evaluate whether the PDS should continue to manufacture lyophilized products.

5d – NIH will write an SOP for the inspection of incoming raw materials, including cleaning supplies by 9/1/15. The SOP will include documentation of events when products fail inspection. The expanded cGMP QA Team will review the events weekly and make recommendations about changing products if necessary. These data will be reviewed every six months with the Chief of the Pharmacy Department and the Deputy Director for Clinical Care, Clinical Center.

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.

Response to Observation 6

The ceiling light bays recently have been evaluated as part of the ORF facility inspection. Visual inspection of the facility identified several breaches in the integrity of the unit; clearly remediation is needed. NIH will also ask the consulting firm to help identify specific remediation plans in the NIH corrective action plan and assure that all future NIH audits address ceiling light bays as well as other aspects of the integrity of the sterile processing environment.

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.

Response to Observation 7:

The PDS previously had corrected the deficiency noted in this observation. As of 4/16/15, PDS is using only the USP Sterility Testing performed in a registered facility. The PDS's current contract is with BioScreen Labs, 3904 Del Amo Blvd, Suite #801 Torrance, CA 90503. Documentation of their SOPs for sterility and pyrogenicity testing are on file in the Pharmacy Department office. PDS will continue to obtain sterility and pyrogenicity tests that follow USP guidelines.

In addition, the PDS has developed a plan to re-test all of the lots quarantined after the inspection using the USP Sterility Test.

1. All lots have been visually inspected (candled), with no evidence of visible contamination detected, and all lots will be sent for repeat pyrogen and sterility testing.
2. PDS began shipping re-testing samples to BioScreen Labs on 5/29/15 and has already shipped approximately 80% of the lots. As the contractor laboratory can perform this test on only 5 lots/day, and since some lots require validation before sterility and pyrogenicity testing, NIH anticipates complete results for these studies by 8/31/15.
3. The Albumin lot #138417 was sent for USP sterility testing on 5/8/15. The 72 vial re-validation test was successfully completed on 5/20/15. An additional 24 vials were sent for sterility testing. No growth was observed in the product from the 24 vials. In addition, this lot has been observed periodically by PDS staff since it was quarantined on 4/16/15, and one of the inspectors visually inspected all remaining vials while they were onsite. In all cases, no particulates have been observed in the remaining vials. On June 11, another 200 of these vials were sent for sterility and pyrogenicity testing.

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.

Response to Observation 8:

a., b. & d. The specific findings in this observation have identified systemic issues. NIH will ask the consultant to review current SOPs to address specific requirements for investigating these events, performing root-cause analyses when appropriate, and assigning corrective and preventive action (CAPA) plans for all events, including microbial failures. With the NIH consultant, NIH will develop a separate SOP for out-of-specification (OOS) events. The cGMP consulting firm will review these SOPs and make specific recommendations for improvement before implementation.

c.ii & iii Formulator LF's bacterial status is clearly trending in a negative direction. The cause could be due to poor gowning technique, to poor aseptic technique or a to a combination of both. The Clinical Center will develop a formal process to assess formulators' performance to identify root-causes for, or contributing factors to, deviations from standard operating procedures. Although this formulator has attended the PDS course on aseptic processing, she and all other formulators will complete remedial training by 8/14/15 and will participate in ongoing competency assessments.

The PDS and the Clinical Center leadership will discuss optimal observational techniques with the cGMP consulting firm and will draft and implement an SOP to periodically monitor the competencies of formulators during batch preparation.

PDS will develop an SOP by 9/1/15 on gowning for aseptic formulation including a checklist that can be completed as formulators are observed gowning.

(Note: the Lidocaine Buffered Lot# 138204 passed sterility testing using the BacTec system, which is what PDS used for sterility testing at that time, before release. PDS can provide clear documentation.)

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.

Response to Observation 9:

NIH appreciates the need for a focused quality control/quality assurance function. NIH will ask the consultant to provide guidance regarding the appropriate structure, function, and authority of the quality assurance/quality control enterprise, including giving consideration to modifications of the current reporting structure. We will also consider increasing the number of QA personnel, pending the results of the consultants review. The responsibilities for observation 9 will be assigned to the expanded cGMP Quality Assurance Team. NIH will discuss all of these items with the cGMP consulting firm and develop the appropriate SOPs by 9/1/15.

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

Response to Observation 10:

The observation that the PDS released a defective product indicates a much broader systemic issue. PDS will create the appropriate SOPs by 9/1/15 to include the proper training needed to do visual inspection that includes details of the process. The SOP will also address the frequency and types of competency assessments for those doing the visual inspections. Separate SOPs will be developed for the processes to follow in instances in which any particulate is discovered, including following the event SOP, defined criteria for releasing or not releasing the batch, and procedures for assessing root causes for the problem. PDS, the Clinical Center, and NIH leadership will work with the contract cGMP consulting firm to explore this observation in more detail to assure that the ultimate response is comprehensive and to assure that SOPs and procedures meet all applicable guidances.

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.

Response to Observation 11:

PDS will identify (by 7/1/15) alternate sterile coverings that provide acceptable coverage of all body areas including the face. Once identified, PDS will procure these coverings, train staff in their use and implement them in accordance with the gowning SOP. This FDA observation has sensitized us to the importance of maintaining adequate barrier supplies as well as instructing staff to bring these types of safety issues forward to their supervisors. As new employees are hired, the PDS leadership will evaluate each individual's protective apparel needs and purchase the necessary equipment. Effective immediately, to ensure that appropriate protective apparel are available each day, designated PDS staff will assess the inventory each evening and order and secure any items necessary to maintain an adequate supply at all times. A checklist will be developed to facilitate this process. To measure whether this activity is being completed as scheduled, the PDS Chief will review the checklists for completion and compliance on a weekly basis.

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.

Response to Observation 12:

Clinical Center and PDS leadership will work with the cGMP consultant to evaluate options including the recommendations "Guidance for Industry, *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products*", that can ensure both the stability and the sterility of our products throughout their expiration dates. Expiration dates will be created consonant with existing FDA guidances. SOPs will be written by 8/14/15 to address these issues.

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.

Response to Observation 13:

NIH is committed to proper initial and periodic cGMP training and competency assessment for all employees who work in PDS.

13a – NIH will work with the cGMP consulting firm to identify potential vendors who can do onsite cGMP training. An SOP will be created for Employee Training that will require all employees' participation in preparing sterile and nonsterile production to receive cGMP training every six months as appropriate to their areas of work; the SOP will include competency measures.

13b – Contract personnel will be trained in the same manner as all other employees in the PDS. They are required to adhere to all PDS policies and SOPs. Competency assessments will be performed in the same manner as all other employees following the PDS SOPs.

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.
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

Response to Observation 14:

a) NIH and the Clinical Center leadership will work with our cGMP consulting firm to evaluate all aspects of lyophilizer production (see response 5b). As part of this evaluation NIH will include options to correct the deficiency related to closure of lyophilized vials.
b) PDS will procure a preventive maintenance and calibration contract for filter integrity testing. NIH will review possible vendor selections with the cGMP consulting firm prior to contracting. The vendor will perform the preventive maintenance at the manufacturer's recommended intervals and will perform calibration at intervals not to exceed 6-months. PDS will draft and implement an SOP by 9/1/15, for performing the filter integrity test and performance of this test will be required for each aseptic lot produced. Documentation review will become a requisite part of each lot record page and require review prior to completing the record.
c) The CC leadership will work with our cGMP consulting firm to create an SOP for media fill simulations. Factors considered for this procedure will include identifying and defining criteria for worst-case scenario setups, including restrictive airflow patterns, turbulent air, most critical or highest number of interventions, longest duration,

greatest number of units, or use of automated equipment. All staff involved in the preparation of sterile products will complete this exercise every six months.

d) The Clinical Center will work with NIH Office of Research Facilities to identify options for maintaining continuous power in the sterile processing area. PDS will develop an SOP by 9/1/15 to address unexpected power failures. The SOP will also provide guidance —– for circumstances in which the PDS power is not continuous —– for the development of cleaning strategies after a failure as well as for facility evaluation before sterile products are prepared after the failure.
e) This observation underscores procedural and competency deficiencies identified by the inspectors as a major item requiring remediation. NIH will address these deficiencies by retraining all individuals, regularly assessing their competencies, and by having all staff participate in competency-based simulation scenarios that intentionally demonstrate improper aseptic technique (including fine points demonstrating improper gowning and improper sterile procedures and precautions) to determine if production staff are able of recognizing specific missteps in the processes. It is possible that staff reassignments will be needed. The Clinical Center will hold employees accountable for their performance and this will be a critical element in each employee's annual Performance Management and Appraisal Plans (PMAPs). An SOP will be developed describing proper aseptic technique and performance in the sterile processing area.
f) After developing a list of sterile components (e.g. vials, stoppers, tubing, needles), PDS staff will work with our cGMP consulting firm to develop SOPs to perform hold-time validation studies for all sterilized components used in the Class 100 aseptic filtration process.

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.

Response to Observation 15:

By 7/1/15, as an initial step to correct these deficiencies, PDS will work to diagram load configurations that represent the range of materials washed and sterilized in the autoclave and oven. The cycle parameters for each respective unit will be documented on the load diagrams. Records of each load will be kept in PDS and reviewed every six months with the Chief, Pharmacy Department and the Deputy Director for Clinical Care, NIH Clinical Center.

PDS will work with the cGMP consulting firm to devise a matrix approach to the load configurations that will adequately cover the different potential materials, loads, and patterns undergoing washing and sterilization. PDS will also use the cGMP consulting firm to develop and execute a validation protocol that would meet current regulatory expectations.
PDS staff have initiated contact with the representative for our vial washer to inquire about its ability to record cycle data. If the exiting machine can be modified to accommodate this request, the Clinical Center will facilitate this improvement. If it cannot be appropriately modified, the CC will obtain a vial washer with this capability.

The autoclave provides a printout record for each cycle. These data will be collected in a logbook and reviewed by the formulators at the end of the cycle, and then by the expanded cGMP QA Team on a weekly basis, as well as prior to approval of a completed formulation record. Summary data will be reviewed every six months with the Chief, Pharmacy Department and the Deputy Director for Clinical Care, NIH Clinical Center.

Connection of recorders to the depyrogenation oven for data collection is already in progress. PDS will work with the current service contractor, Quality Process Solutions (QPS), to evaluate the oven and install the necessary hardware to collect these data. These data will also be recorded in a logbook and reviewed by the formulators at the end of each cycle, by the expanded cGMP QA Team on a weekly basis, as well as prior to approval of a completed formulation record. Summary data will be reviewed every six months with the Chief, Pharmacy Department and the Deputy Director for Clinical Care, NIH Clinical Center.
An SOP will be established for data collection, reporting, and review for each of these three devices.

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 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.

Response to Observation 16:

a. PDS will develop an SOP for sampling and monitoring the water for injection (WFI) supply to include microbial testing. A suitable laboratory will be identified for microbial testing.

The SOP will be written by 9/1/2015 and the process will be in place and documented as effective prior to resuming sterile product production in PDS. These data will also be collected, kept in a logbook and reviewed by the formulators at the end of each cycle and by the expanded cGMP QA Team, both on a weekly basis as well as prior to approval of a completed formulation record. Summary data will be reviewed every six months with the Chief, Pharmacy Department and the Deputy Director for Clinical Care, NIH Clinical Center.

b. PDS acknowledges the regulatory requirement to perform both initial (validation) and routine chemical (pH, conductivity, total organic carbon [TOC]) and microbiological (endotoxin and sterility) testing of the WFI produced in the facility. PDS and the Clinical Center will work with our cGMP consulting firm and our facility personnel to modify our existing system, to create an SOP, to validate the SOP, and to incorporate these procedures into our daily routines as required by FDA.

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.

Response to Observation 17:

PDS leadership acknowledges that container closure integrity testing required to ensure product sterility and integrity was not performed as part of our processes. PDS will work with our cGMP consulting firm to develop an optimal solution to this problem, to develop an SOP to implement this solution in order that we can become compliant with this observation.