NIH Interim Corrective Action Plan in
Response to Inspectional Observations Dated May 29, 2015 of the
NIH Clinical Center Pharmacy

The NIH leadership thanks the Food and Drug Administration (FDA) investigators for their thoughtful observations during the inspection of the National Institutes of Health Clinical Center's (NIH CC) Pharmacy Intravenous Admixture Unit which concluded on May 29, 2015. The Pharmacy Department and the NIH CC leadership as well as the NIH leadership take the investigators' observations very seriously and the senior leadership is committed to taking all necessary measures to ensure the safety of all research participants and correct all deficiencies.

The Investigator's observations have identified several systemic issues that will require us to address facility, human factors, and department organizational culture issues. The facility issues will be addressed by engaging NIH staff and outside consultants. Addressing the human factors and the department organizational culture issues on a broad scale will assure compliance with the proper procedures (i.e. no exposed skin during preparation) for preparing sterile products. When combined, these improvements will address all of the concerns delineated in the FDA inspection 483 report.

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Observation #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.

Response: We recognize that remediation requires more than simple training for this individual. The observation reveals a systemic problem that needs to be addressed with training, competency assessment, and department organizational culture changes.
The NIH CC Pharmacy Department has policies to address proper attire for the anteroom and the clean room buffer area. All IV Admixture Unit staff were trained recently (January-June 2015) in the USP <797> process using a new web based Simplifi 797 training program, a comprehensive training program that covers knowledge about USP <797>, proper aseptic technique, and hazardous drug compounding. In the future all new hires will be required to complete this training prior to working with sterile preparations. The program includes written materials as well as video demonstrations of proper technique. Successful completion of this training requires satisfactory completion of an exam. An exam score of 80% or better is required to pass the training. The deficiency noted in this observation demonstrates that this training alone is not sufficient to ensure that employees understand and practice the requirements to protect drug products from contamination. In response to this FDA observation, we also provide the following actions:

- Upon questioning the employee observed, it was determined that neither the proper size gown nor beard covers were available for use on the day of the FDA inspection. Upon questioning two other technicians, both stated they would have used alternative size gowns (bigger). One stated that they would not feel comfortable telling the pharmacist that they did not have the necessary equipment to work in the IVAU. The other was comfortable with speaking with the pharmacist and pursuing an appropriate solution, even if it were necessary to borrow equipment from a local hospital. We have since obtained beard covers through Pharmacy's Procurement section. The section chief will ensure that gown sizes appropriate for this individual and others are available. 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 IV Admixture Unit 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 pharmacy 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 Inpatient Section Chief will review the checklists for completion and compliance on a weekly basis.

- All operators are required to complete sterile compounding training using the Simplifi 797 training program at the time of orientation to the IV Admixture Unit and now every six months. These observations demonstrate that the training program alone is insufficient to ensure proper sterile product preparation. Starting the week of June 8th, all employees will begin re-training regarding proper IV Admixture Unit attire using the modules of the Simplifi 797 program that specifically address this area. In addition, the IV Admixture Unit leadership will develop a practical competency assessment to test each employee after the didactic training. Employees will be required to pass this competency before preparing sterile products. This effort is expected to be completed by July 1, 2015 for all staff involved in the preparation of sterile products. Once the remedial training is completed, staff producing sterile products will be required to re-certify every six months. Records for these re-certifications will be maintained in the Pharmacy Department and reviewed every six months by the Chief of the Pharmacy and the NIH CC Deputy Director for Clinical Care.

- These observations (e.g., deviation from standard operating procedures, lack of peer-to-peer feedback, and failure to bring safety concerns forward to peers and supervisors) indicate that there are human factors and department organizational culture issues influencing staff performance; including normalization of deviance, the presence of authority gradients and communication barriers, and a reluctance to report variance from standard procedures. To raise awareness regarding these issues and to provide staff with tangible and practical approaches to remove the influence of these factors and mitigate the potential for error and research participant harm, the NIH Clinical Center Patient Safety and Clinical Quality staff will design and deliver a customized "Culture of Patient Safety" training program for all Pharmacy staff. This training will allow staff to understand the importance of their contribution in maintaining compliance with policies and procedures as well as in improving pharmacy processes. This training will begin in the IV Admixture Unit the week of June 15th and will be repeated annually. All new employees will be required to complete this training.

- The Pharmacy quality assurance/quality improvement (QA/QI) structure and function will be reviewed with the intent of enlarging the QA/QI team and modifying reporting relationships of the team to assure objective continuing review.

- Pharmacy management understands that retraining alone is not sufficient and direct observations of technique must be assessed on a continual basis to ensure compliance with proper aseptic technique.

- The IV Admixture Unit leadership will develop competency-based simulation scenarios that intentionally demonstrate improper aseptic technique, including fine points of improper gowning, to determine if technicians and pharmacists are able to recognize

specific missteps in the process. Also, pharmacy department employees and outside consultants, after proper training, will be used to do periodic announced and unannounced audits (initially every other week) to assess compliance with proper technique. Observations, both of exemplary compliance and non-compliance, will be reported to the IV Admixture Unit supervisor who will correct deviations immediately and track deviations for corrective action and trends. Deviations from accepted procedures will be communicated immediately to the Chief of Pharmacy who will communicate these directly to the Deputy Director for Clinical Care. Quarterly audits will be conducted for the on-going assessments.

- To improve and measure aseptic technique performance for both hazardous and non-hazardous medication, the frequency of assessments for media fill competency using the Valiteq ChemoTeq system will increase from annually to every six months.

- Full documentation of training, post-test records, and deviations will be maintained within the Simplifi <797> software by the expanded QA/QI team and reviewed by the Chief of the Pharmacy and the Deputy Director for Clinical Care quarterly for trends.

- Employees working with sterile product preparation will be held accountable for proper aseptic preparation as a performance measure in their yearly evaluations and their performance measures will be a critical element in their annual Performance Management and Appraisal Plans (PMAPs). As described above, metrics will be collected for performance evaluations and the annual performance appraisal process will include data-driven assessments of compliance with sterile product compounding competency (based on the metrics described above) as well as compliance with required procedures.

Observation #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 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.

Response: Although the hoods were recertified in April 2015, dynamic airflow studies were not part of the certification process. Dynamic airflow studies will begin by July 1, 2015 and will be completed within 45 days for all individuals preparing sterile products. Results will be forwarded as soon as they are available. In addition, the following specific interventions will be implemented:

- The ISO 5 horizontal hoods will be added to the list of biological safety cabinets that undergo airflow pattern studies every six months by ENV Services, Inc.

- Dynamic airflow studies will be conducted every six months and will be the responsibility of the expanded QA/QI team and the hood certification contractor (ENV Services, Inc). 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 the IVAU's biologic safety cabinets. NIH will extend this contract to include dynamic smoke studies for all hoods and all operators in the sterile processing area the IVAU. These studies will be conducted with every individual producing sterile products. Studies for each operator will be conducted and videotaped every six months. The Pharmacy policy will be updated with this change in procedure and the frequency of testing.

- The Chief of the Pharmacy Department met with the Corporate Training and Technical Manager of ENV Services, Inc., the current hood certification contractor for the NIH campus, on June 2, 2015. ENV Services, Inc. is able to do the dynamic airflow pattern studies. Videotaping of this process will be included.

- The Inpatient Section Chief will be responsible for confirming that the airflow studies are completed and repeated every six months. Documentation will be maintained in the Simplifi 797 system and records will be reviewed every six months with both the Chief of the Pharmacy Department and the Deputy Director for Clinical Care to assure compliance with ISO 5 standards of air cleanliness.

- In instances in which problems with these airflow studies are identified, the individual being assessed will not be allowed to participate in sterile production until the problems can be resolved.

Observation #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

Response: The process for disinfecting the ISO 7 and ISO 5 areas (preparation hoods) will now include a sporicide as described below:

- Sterile isopropyl alcohol and a germicidal agent (Asepticare TB+II) are currently used as per USP <797>. In addition, we will use a sporicidal agent once daily.

- 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 for the IVAU. Working with the consulting firm, NIH will create a written SOP by 7/1/15 to address proper use and protection when using a sporicidal agent, proper hood cleaning, and documentation procedures, including the documentation of the efficacy of the sporocide.

- We initiated the procurement process of purchasing Steriplex SD as of June 3, 2015. We have identified an alternate EPA registered sporicidal, Peridox, in the event Steriplex SD is not available.

- We will do just-in-time training of staff the week of June 15th, 2015 and start using the sporicidal agent as soon as it arrives. Training in the use of disinfecting agents (including the sporicidal agent) will be incorporated into the every-six-month ongoing training program and will be documented for each employee undergoing training in the Simplify <797> software.

- The proper use of a sporicidal has been incorporated into the Pharmacy Department policies and procedures. The IV Admixture Unit Supervisor is responsible for evaluating and documenting compliance with these procedures. Data will be reviewed weekly for deviations and trends and for assuring that post-use assessment documents the efficacy on the use of the sporocidal agent. These data will be reviewed every six months with the Chief of the Pharmacy Department and the Deputy Director for Clinical Care.

Observation #4: Drug product operations and procedures are not performed in specifically defined areas of adequate size to prevent contamination or mix-ups. Specifically, facilities were not designed and controlled to prevent contamination risks to sterile drugs in that:

a) There is inadequate separation of the processing area from the common pharmacy and uncontrolled flow 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 IV Additive Unit 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**.

Response: In 2014, the Chief of the Pharmacy Department identified the current design as a potential risk point and requested a proposal for redesign the IV Admixture Unit to assure proper chemotherapeutics preparation, to comply with current <USP 797> Standards, and in

anticipation of the new proposed <USP 800> Standards. In December 2014, a proposal for a new design was obtained from Amick Medical Systems. The plan is to create a statement of work to determine what other designs may be alternatives to the one provided by Amick Medical Systems. The facility correction is expected to be extensive.

- As an immediate, but temporary measure until the facility redesign has been implemented, uncontrolled flow of staff from the IV Admixture Unit to the common pharmacy space will be controlled by all of the aspects of training, competency assessment, and observations delineated in our response to Observation #1. Pharmacy leadership will also work with NIH Office of Research Facilities, the NIH Fire Marshall, and the CC Environmental Safety Officer to determine if a temporary solution can be implemented without compromising air flow in the IV Room. Confirming that personnel flow does not compromise the maintenance of aseptic technique will be included in the observations and competency assessment included in the response for observation #1.
- By June 26, Pharmacy leadership will evaluate possible temporary solutions for preparing chemotherapy (e.g., incorporating the use of isolators) in the IV Admixture Unit.

- For the facility redesign process:

    - Pharmacy leadership will formally review the proposed design of immediate and long term renovations with the Office of Research Facilities leadership by June 19, 2015.
    - By July 15, after gathering all necessary information, NIH Clinical Center leadership, Pharmacy Department leadership and the NIH Office of Research Facilities will develop an action plan to redesign the area to meet all required standards.