

Report from NIH Task Force on the Clinical Center Pharmaceutical Development Section (PDS)

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NIH Task Force on the Clinical Center Pharmacy Department

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NIH Task Force Membership

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Summary of Major Points

- FDA inspection and subsequent internal assessment by the NIH PDS Task Force revealed longstanding and multifaceted problems in the Clinical Center Pharmacy's sterile operations
- Short term remediation measures are in place for the Pharmacy Intravenous Admixture Unit (IVAU); long term remediation will be required to come up to current compliance standards
- The Pharmaceutical Development Section sterile operations (PDS) section has been shut down due to the serious deficiencies outlined in the FDA inspection reports (Form 483); the solid dose (non-sterile) portion of the PDS has continued operations, albeit in a more limited manner
- We continue to seek alternate sources for products formerly prepared in the PDS; going forward all product requests will be prioritized
- Fortunately, to date, there is no evidence that any research participant has been harmed by any PDS-prepared product

2015 Timeline

- May 19-29: FDA unannounced “for cause” inspection of CC Pharmacy
- May 22: CC Director placed PDS sterile manufacturing on hold
- May 29: Two FDA Form 483’s received. Observations included problems with facilities, SOPs, and personnel training
- June 4: NIH posted the 483s and announced that PDS sterile operations were suspended
- June 9: NIH Director convened internal Task Force
- June 19: NIH submitted an Interim Corrective Action plan to FDA
- July 1: Pharmacy Director and PDS Director moved to other Clinical Center positions
- August 11: External consultants presented a draft report to NIH (final 10/8)
- September 17: NIH met with FDA on remediation update
- November 18: NIH compliance office planning team convened
- December 3: NIH Task Force presented its findings to NIH Leadership
- December 10: NIH Task Force presents its findings to the ACD
- January 2016: NIH will convene an ACD Working Group chaired by Norm Augustine

PDS FDA Observations, 5/29/15 (1)

Training:

- No GMP training program in place

Facilities:

- Air system not adequately designed and controlled
 - Positive air pressure not maintained
 - Failed to demonstrate unidirectional flow
 - Frequent service interruptions and failures
- Exhaust vent, opening directly to roof many floors above, with no filter located above the autoclave discharge
- Insects in the ceiling light bays, gaps in the caulking

PDS FDA Observations, 5/29/15 (2)

Sterile Procedures:

- Gowning/protective apparel not correctly worn, personnel not maintaining sterile practices
- Insufficient microbial, particle and environmental monitoring; alarms were disabled
- Investigations into non-sterility were not appropriately conducted and resolved
- Inadequate visual inspection of sterile products by staff

PDS FDA Observations, 5/29/15 (3)

SOPs:

- Cleaning protocol doesn't include sporicidal agent; cleaning of hoods not always documented
- Sterility testing method not validated
- No written stability testing SOP

Quality Control:

- Quality control unit has insufficient authority and oversight of approval/release of products, IND formulation records, sterilization cycles, and deviations in protocols

NIH Response 6/4/15: Collins Statement

“This is a distressing and unacceptable situation.”

“The fact that patients may have been put in harm’s way because of a failure to follow standard operating procedures in the NIH Clinical Center’s Pharmaceutical Development Section is deeply troubling. I will personally oversee the steps to protect the safety of patients and remedy the situation as swiftly as possible.”

“NIH leadership is determined to identify and correct all of the deficiencies that have led to this situation.”

NIH Response

- NIH Task Force (established 6/9)
 - Contract organization engaged to independently assess the PDS and IVAU, and recommend remediation approaches
 - Provided FDA interim corrective action plan (6/19)
 - Developed short-term remediation for ongoing operations
 - Continue to work closely with FDA on current protocols
 - Proposed creation of new Quality Assurance Office reporting to the Deputy Director for Intramural Research

NIH Response: Interim Corrective Action Plan to FDA (6/19)

Overall:

NIH will retain a contract organization to independently evaluate all aspects of the FDA's observations and make recommendations about remediation

Specific Elements to be Evaluated:

- **Facilities**
 - Evaluate air handling and implement SOPs for testing air flow
 - Evaluate the deficiencies of facilities and equipment and whether new facilities or equipment are needed
- **Training**
 - Establish routine cGMP training programs including ad hoc testing for all staff involved in sterile production
- **SOPs**
 - Identify and develop needed SOPs
- **Quality Assurance/Control**
 - Seek guidance on the role of the QA/QC components

NIH Response: Independent Contractor Assessment

- Conclusions of Tunnell Consulting (10/18) - expanded upon observations made by FDA in 483 Forms
 - There were many deficiencies in the PDS that could have led to contamination
 - To achieve cGMP capabilities in the current facilities, a major rebuild of the PDS and Pharmacy would be required
 - ~\$50M for the PDS and \$20M for the Pharmacy and 16-18 months
 - The facilities did not meet cGMP at the time of opening in 2010
 - Of the ~150 SOPs required, only 11 final and 15 in draft, were in place
 - Training was inadequate
 - Organization and leadership structure was not conducive to effective QC/QA

NIH Response: NIH Task Force Analysis of Affected Protocols and Participants

- Over 100 current NIH research protocols used PDS products
- Immediate concern for participant safety
 - Monitoring and retrospective clinical analysis
 - No evidence of harm to current or past participants
- Retesting of all quarantined products
- Clinical Center and NIH OHSRP tracked protocol status
- Principal Investigators reported to FDA, the HHS Office for Human Subjects Research Protections, and notified participants

NIH Response: Identification of Product Sources

- Commercial sources if available (e.g. pentastarch cryopreservative)
- FDA allowed use of quarantined products on a case by case basis
- A few investigators have identified alternative production facilities
 - It has proven difficult to identify alternative facilities that are FDA-inspected and can that produce the specialized products needed
 - NIH is setting up a contractor to conduct inspections of alternative sources
- Production at the NCI cGMP facility in Frederick
 - Capacity and timeline depends on product complexity. MOU in development
 - 9 PDS personnel are being retrained at Frederick – 5 month process
 - Equipment is being moved from PDS to NCI Frederick – will need reassembly, calibration, and certification before use
- NIH/OIR is working on process for prioritizing products

NIH Task Force Study Reveals History of Problems with PDS

- Before the PDS opened, problems with facilities, SOPs, and training were documented multiple times. These included a comprehensive evaluation by a contractor in 2009, and internal tracking. These problems were never fully resolved.
- There is no documentation of cGMP compliance before PDS opened in 2011.
- Multiple problems with air handling, cleaning/disinfecting, SOPs, and training documented after the PDS opened.
- FDA conducted an informal “walkthrough” of the PDS in 2012 and discussed a possible “for cause” inspection that was never conducted.
- FDA noted that there were at least 4 contamination events in 2014-2015. These were confirmed in interviews with PDS staff.
- There was inadequate communication by Pharmacy/PDS leadership to CC leadership about the approaches to, and challenges in, meeting cGMP compliance

Office of Research Support and Compliance

- Scope being determined:
 - FDA regulations, human subjects protections, biospecimens, etc.
- It should serve as a central knowledge resource
- Ongoing:
 - Inventory and gap analysis of central and IC compliance activities
 - Exploring models at academic research institutions

Congressional Oversight Investigation

- Both House E&C and Senate HELP launched oversight investigations into shutdown of PDS
 - Numerous briefings by NIH staff and leadership, as well as documents provided between June and November, 2015
 - House E&C O&I subcommittee is very focused on impact on individual research participants and protocols
 - Senate HELP discussions led to formation of “Red Team” – ACD Working Group
- Appropriations Chairs and staff have also been briefed

Clinical Center Working Group of the Advisory Committee to the Director (ACD)- I

- **Charge:**
 - Make recommendations on organization, financing, management to reduce risk for clinical research activities
 - Examine structural and cultural issues underlying failures
 - Review other activities of potential risk to participants
- **Convenes in January; report expected spring 2016**

Clinical Center Working Group of the Advisory Committee to the Director (ACD)- II

Membership:

- Norm Augustine (chair), former CEO, Lockheed Martin
- Victoria Christian, CEO, Duke Translational Research Institute
- Laura Forese, President, New York-Presbyterian Healthcare System
- Donald Gagliano, Principal, Global Medical Innovation, Walter Reed National Military Medical Center
- Harlan Krumholz, Yale School of Medicine, ACD
- Kurt Last, Founder and former CEO, Specialty Operations Solutions, Inc.
- Richard Marchase, VP for Research, University of Alabama at Birmingham
- Edward Miller, former CEO, Johns Hopkins Medicine
- John Noseworthy, President and CEO, Mayo Clinic
- *Ex officio:*
 - Kathy Hudson, Deputy Director, Science, Outreach and Policy, NIH
 - Lawrence Tabak, Principal Deputy Director, NIH

Next Steps

- We must bring the Pharmacy (IVAU) up to proper standards.
 - Search for new head of Pharmacy
 - Move to another location in CC or rebuild in place?
 - Must allow for ongoing operations
 - Must ensure remaining in compliance going forward
- We must decide if we want an NIH cGMP facility or if we want investigators to outsource their product needs
 - Will NCI Frederick, outsourcing and prioritization of protocols be adequate for meeting needs of investigators?
- Creation of an Office of Research Support and Compliance within the Office of the Director, Office of Intramural Research
- Response to ACD WG Recommendations

Summary

- Longstanding and multifaceted problems have been identified in the Clinical Center Pharmacy's sterile operations
- Short term remediation measures are in place for the IVAU; long term remediation will be required to come up to current compliance standards
- Sterile activities within the PDS remain closed; the solid dose (non-sterile) portion of the PDS has continued limited operations
- We continue to seek alternate sources for products formerly prepared in the PDS; going forward all product requests will be prioritized
- Fortunately, to date, there is no evidence that any research participant has been harmed by any PDS-prepared product