

NIH Task Force on the Clinical Center Pharmacy Department

Committee Charge: In response to observations from a Food and Drug Administration (FDA) inspection of sterile processing components of the Pharmaceutical Development Service (PDS) and the Intravenous Admixture Unit (IVAU) in the Clinical Center Pharmacy at the National Institutes of Health (NIH), NIH Director Francis Collins convened an internal Task Force to investigate the deficiencies that were identified, and provide guidance and oversight for the NIH response. NIH elected to suspend sterile processing in the PDS and to implement interim remediation measures to enable ongoing operations in the IVAU. To ensure participant safety, mitigate interruptions in research, and provide a foundation for long-term remediation strategies, the Task Force was charged with the following:

- Monitor the status of affected protocols and participants
- Facilitate identification of alternative sources of sterile products
- Coordinate with the FDA, the HHS Office of Human Research Protections (OHRP), and institutional review boards (IRBs)
- Conduct an assessment of problems with facilities, management, training and procedures in the PDS and IVAU
- Review and approve interim remediation plans
- Coordinate communications with Congress, the press, participants and others

The Task Force met on a weekly basis from June 9, 2015 until October 20, 2015, and delivered its report to the NIH Director on November 25, 2015.

Task Force membership

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Background: The PDS formulates and packages batches of investigational drugs and other research products for use in research protocols at the NIH Clinical Center. The IVAU formulates and packages sterile products on a case-by-case basis to fulfill medical prescriptions for individual participants and patients while they are at the Clinical Center. FDA conducted an inspection of the NIH Clinical Center Pharmacy Department between May 19 and May 29, and reported a number of deficiencies in the PDS and IVAU. The FDA observations included problems with facilities, personnel training, and standard operating procedures in both units. NIH suspended sterile operations of the PDS on May 22 and posted the FDA observations on June 4.¹ Because the FDA observations in the IVAU were less serious, NIH has been able to maintain IVAU operations during the course of ongoing remediation efforts.

The FDA inspection occurred after the report of fungal contamination of two vials of albumin in the PDS in April. FDA's observations and the NIH Task Force's assessment over the course of the summer revealed that the underlying problems were widespread and longstanding.

Affected protocols and participants: At the time of the PDS suspension on May 22, over 100 current NIH research protocols used products that were prepared in the PDS. The Task Force worked with the Clinical Center and the NIH Office of Human Subjects Research Protection to track the status of all of these protocols. Participant safety was the predominant concern. We requested a risk analysis and a two-year retrospective clinical analysis to determine if any Clinical Center patients had been harmed by exposure to PDS products. Based on this assessment and ongoing monitoring of current participants, we have found no evidence of any direct harm to past or current participants. To ensure that all researchers knew what steps to take, we developed and disseminated guidance on participant notification, reporting to FDA and OHRP, and obtaining safe products.

Product sources: Since the suspension of sterile processing in the PDS and quarantine of existing PDS products, the identification of alternative sources for the research products previously formulated in the PDS has been a major priority. Many of the protocols were put on partial clinical hold while investigators worked to identify alternative product sources. The Task Force tracked interruptions in protocols and assisted in communications between investigators and the FDA about quarantined PDS products or alternative sources.

About half of the affected protocols were cell therapy studies that used a cryopreservative dispensed by the PDS. These studies are managed by the NIH Department of Transfusion Medicine. The cryopreservative is available commercially, so there was no interruption in the supply of cryopreservative for these protocols. However, some cell therapy research participants did require immediate treatment. Based on evaluation of risks and benefits, the FDA allowed use of the quarantined PDS product (i.e. with cells already mixed with the PDS-dispensed cryopreservative) on a case-by-case basis for individual research participants.

For the remaining protocols, the Task Force has assisted in the process of identifying sources for products previously formulated in the PDS. Investigators have switched to commercial sources when available. NIH is establishing an ongoing contract to vet external compounding facilities for products that are not commercially available. We are also assessing the capacity and timeframe for production of some of the PDS-formulated products in the National Cancer Institute's Pharmaceutical Management Branch (PMB), located in Frederick, MD.

¹ <http://www.nih.gov/news-events/news-releases/nih-suspends-operations-its-clinical-center-pharmaceutical-development-section>

In recognition of the limited capacity of the NCI facility and other sources, the Task Force has recommended that the Office of Intramural Research establish a systematic prioritization process for future product requests. While initially the number of participants scheduled to receive a PDS product was very small and could be handled with individual risk assessments and waivers, as time goes on, more participants will be scheduled for products. In addition, investigators developing new protocols will need to know where to seek products and what constraints exist. Ongoing responsibility for tracking research needs and product sources has been transitioned from the Task Force to the NIH Clinical Center and the NIH Office of Intramural Research.

External assessment of PDS and IVAU facilities: In order to understand the extent of the problems in the PDS and IVAU, early on in our tenure the Task Force commissioned an assessment by an experienced cGMP contractor, Tunnell Consulting. We charged Tunnell with assessing the specific nature of the problems with facilities, training, and procedures, and to make recommendations on short-term and long-term remediation. After conducting site visits and interviews with the Pharmacy Department, Tunnell delivered its report to the Task Force on August 11, 2015. The report contained a review of the FDA observations, additional observations of shortcomings related to facilities, training and procedures, and recommendations for remediation. Many of the short-term remediation recommendations have already been initiated. We learned from the Tunnell report that the extent of the problems would necessitate significant facility construction for both the PDS and IVAU to meet modern requirements for cGMP compliance. Additional decisions still need to be made about how to address long-term remediation of facilities (including the potential need for new construction); these decisions will rely on additional information about alternative options and consultation with other external experts.

Internal investigation: The Pharmacy Department problems brought to the attention of NIH leadership initially because of an isolated contamination event turned out to be the result of a systemic set of failures that date back to before the current PDS facility opened in 2011. The scope of our assessment shifted from simply understanding the current remediation needs to assessing the underlying issues that led to these problems. The Task Force members and staff reviewed documents related to the construction and establishment of the pharmacy facilities, held interviews with relevant staff, and reviewed emails between pharmacy leadership and staff. Our investigation revealed that the underlying issues were more serious and widespread than was initially understood. For example, the PDS website states that it is a cGMP facility; but even at its construction, it was not designed to meet cGMP requirements for all of the types of products that were planned. We learned that there was a prior history of contamination events and a systematic failure to adhere to a set of standard safety and compliance principles. Instead, priority had been put on producing a high volume of products to meet the requests of intramural investigators. Overall, we found that there was insufficient cGMP and regulatory expertise within the Pharmacy Department. The findings from this internal investigation contributed to the NIH decision to create a new compliance oversight office that will coordinate research oversight activities across NIH, promulgate policies, and serve as a hub for expertise and training on regulations and research quality.

Coordination with FDA and OHRP: Task Force members and staff have been in frequent, at times daily, communication with the FDA since the issues came to our attention at the end of May. Investigators with products that were subject to Investigational New Drug monitoring by the FDA were required to file safety reports with FDA and all protocols were required to file unanticipated problem reports with OHRP. We sought clarification on reporting requirements, and as noted above, provided guidance and template language to investigators to assist them in their direct communication with FDA and OHRP. Based on this guidance, investigators continued to communicate directly with FDA on waivers to use quarantined PDS products and approval to amend protocols to include products from alternative sources.

To respond to FDA expectations, the NIH Clinical Center developed an interim corrective action plan for the PDS and IVAU, which the Task Force reviewed and submitted to FDA on June 19, 2015.² We subsequently shared the Tunnel findings (see above) and reported on our progress at a meeting with FDA staff on September 17, and submitted an update on short-term remediation activities on October 22. The focus of this update was on the changes that have been implemented to enable ongoing operations in the IVAU.

Responding to Congressional and other inquiries: There has been significant Congressional interest in the PDS and IVAU. The Co-chairs and staff of the PDS Task Force have responded to inquiries about the status of participants and protocols, the issues that led to problems, and the NIH response. Task Force members and staff have provided information and briefed members of both the House and the Senate on all aspects of the NIH response. We take the problems in the PDS and the IVAU very seriously, and acknowledge the concerns of our oversight and funding committees.

Next steps: As we transition beyond an immediate response, NIH leadership must turn its attention more fully to the long-term needs of current and future protocols. The Clinical Center and the Office of Intramural Research will now be responsible for ongoing protocol oversight and remediation activities. The NIH Office of the Director will continue to facilitate communication between the NIH and FDA. In addition, the NIH Director has assembled an external group of advisors to inform the NIH on enhancing management of the Clinical Center to improve overall quality, safety and compliance for research involving human subjects. Their recommendations will include the PDS and extend to other activities at the Clinical Center. The NIH Task Force members may continue to advise NIH leadership on an *ad hoc* basis during continued corrective actions in the Pharmacy Department and broader remediation of human subjects research compliance activities.

² <http://www.cc.nih.gov/phar/pdfs/NIH-Interim-CAP-Pharmacy.pdf>