



NOV 16 2015

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Upton:

Thank you for your September 29, 2015, letter expressing your continued interest in our response to the suspension of the operations in the aseptic unit of the National Institutes of Health (NIH) Clinical Center Pharmaceutical Development Section (PDS). I want to assure you that our highest priorities in this matter are to safeguard the well-being of the research participants who are enrolled in the clinical studies that used PDS products and to find alternative sources, as appropriate.

Please find enclosed responses to the questions in your letter. If you have any further questions going forward, please let me know.

I will provide a response to Representative Murphy under separate cover.

Sincerely,

A handwritten signature in cursive script, appearing to read "Francis S. Collins".

Francis S. Collins, M.D., Ph.D.
Director

Enclosure

cc:
The Honorable Frank Pallone, Jr.
The Honorable Diana DeGette

- 1. What is the status of each of the patients since the experimental treatments were stopped? Have any patients died since the treatments were stopped? If so, how many? What is the emotional status of all patients still alive?**

There are 61 current protocols that use a product that was formulated in the NIH Clinical Center Pharmaceutical Development Section (PDS). There are 53 other protocols involving cells prepared in the Department of Transfusion Medicine (DTM) that used pentastarch cryopreservative from PDS. The DTM protocols have all either received waivers on a case-by-case basis to use cells already processed with PDS pentastarch or obtained an alternative source of pentastarch. As such, we have excluded the 53 DTM protocols from our responses to the rest of the questions. Please also note that in our previous communications to you, one DTM protocol was incorrectly listed as a PDS protocol. The actual number of PDS and DTM protocols is 61 and 53, not 62 and 52 as reported previously.

In 29 of the 61 PDS protocols, a total of 234 participants had been scheduled to receive products between the suspension on May 22, 2015 and October 7, 2015 (please see responses to question 2 for further information about these 234 participants). In the other 32 PDS protocols, no participants were scheduled to receive product and further recruitments have been postponed until alternative sources become available. The NIH is assisting investigators to identify alternative sources for current participants who will be due to receive products in the upcoming months and for new participants enrolled in the future.

The numbers presented here are a snapshot and are in flux on a daily or weekly basis as ongoing protocols progress. In some cases, new participants are enrolling, participants are completing their participation, or other changes occur unrelated to the PDS suspension.

Study investigators continue to monitor all participants, and no suspicious adverse events have arisen. Seven participants in five of the 61 protocols have died since May 22, 2015. Causes of death were: cancer (2 participants), alcoholic liver disease, cardiac failure, Menkes disease in infant, graft failure, and lung infection. There is no evidence that study participation, study interruption, or the PDS product played any role in the deaths of these participants (the participant with the lung infection was diagnosed before enrolling in the study). Of the 5 protocols, 3 continued without interruption by getting waivers or alternative product sources; one was amended to exclude the PDS product from renal function testing; and one is on hold because a viable alternative has not been identified (eye dropperette packaging).

- 2. How many patients are currently not getting their study treatment? How many patients had the study treatment withheld but have since been able to resume getting the treatment? Of those patients, how many were able to get the treatment because of a waiver from FDA and how many were able to get the treatment because alternative sources were found?**

In 16 of the 29 protocols with participants scheduled to receive a PDS product, 110 scheduled participants got products either from PDS or from an alternative source.

- 7 protocols got Food and Drug Administration (FDA) waivers to use quarantined PDS products on a case-by-case basis (37 participants total got waivers).
 - Chen, 13-C-0080, 1 participant.
 - Dunavin, 15-H-0088, 1 participant.
 - Gafni, 07-D-0016, 16 participants used product under waivers. Participants are in the process of being weaned off PDS product and transferred to standard treatment. 3 participants left the study to get a similar commercial treatment recently approved by FDA. The study is terminating, but all data is still usable and publishable.
 - Hickstein, 10-0C-0174, 1 participant.
 - Kaler, 09-CH-0059, 16 participants.
 - McDermott, 09-I-0200, 2 participants.
 - McDermott, 14-I-0285, 5 participants got waivers; 1 more had randomization/participation delayed until an alternative was secured and will now continue in the protocol.
- 8 protocols have been using products from alternative sources. In addition, one protocol listed above (McDermott, 14-I-0285) is now using an alternative source after initially using PDS products under a waiver (65 participants total got products from alternative sources, including one participant in the McDermott protocol 14-I-0285).
 - Bishop, 08-EI-0169, 12 participants got a product from an alternative source; 2 additional participants needed another drug for which an alternative has not yet been identified so these 2 participants cannot continue in the protocol.
 - Conlon, 12-C-0113, 1 participant.
 - Cukras, 11-EI-0263, 1 participant.
 - Leggio, 08-AA-0178, 2 participants. 1 participant received a PDS product the week of the suspension, before the formal waiver process was established.
 - Reich, 11-N-0116, recently secured alternative. 2 participants.
 - Venditti, 04-HG-0127, 3 participants.
 - Wiley, 12-EI-0042, 44 participants.
 - Zarate, 14-M-0085, 1 participant.
- 1 protocol used a PDS product that does not need to be sterile.
 - Goldstein, 03-N-0004, 4 participants total, 2 participants received product after risk/benefit analysis determination: topical acetylcholine application does not require sterility but was made in sterile unit for historic reasons because of previous uses in other protocols. Acetylcholine is used to test nervous system function, and is not a study intervention. All participants continued in study.

In 6 of the 29 protocols, participants continued in other portions of the protocol, or the protocol was amended to exclude the PDS product:

- Brown, 13-DK-0057, 3 participants (PDS product portion on hold).
- Etzion, 15-DK-0100, 21 participants.
- Nelson, 12-DK-N151, 33 participants, using other methods to measure renal function.
- Ramsden, 11-AA-0028, 1 participant (also seeking an alternative to continue the PDS product portion).

- Robey, 12-H-0078, 1 participant did not receive product (used in an experimental supplement procedure during surgery). The Principal Investigator (PI) sought permission from the NIH to use the PDS product (non-IND) and was denied because of risk/benefit analysis. Protocol was subsequently amended to exclude PDS product.
- Skarulis, 07-DK-0077, 5 participants.

In 5 of the 29 protocols, the NIH is seeking an alternative source for current participants. Participants are receiving clinical standard of care while at the NIH or from their regular physicians:

- Brown, 15-DK-0119, 4 participants.
- Chung, 13-H-0123, 13 participants.
- Connors, 14-I-0011, 5 participants.
- Delaney, 13-CH-0139, 2 participants.
- Schrump, 14-C-0053, 12 participants. PI determined safer to remain on hold until alternative is secured.

2 of the 29 protocols are on hold and no alternative has been identified, participants are receiving clinical standard of care:

- Datiles, 13-EI-0206, 15 participants. No viable alternative source is available for the specialized packaging required by the protocol.
- Ward, 13-AR-0056, 4 participants had intervention interrupted and cannot continue in the study.

3. Have all patients been contacted about the status of their study?

All participants who received product from the PDS since the suspension have been notified, except for participants enrolled in the Goldstein protocol. It involved a topical product that does not need to be sterile.

PIs are in the process of notifying past participants who might still be at risk for manifesting a latent infection, i.e., participants who received a product since January 1, 2015. These notifications are nearly complete.

4. What is the status of each patient's study? Are they in treatment? Were the studies they were enrolled in showing any positive signs of success? If there were positive results coming out of any studies for any patients, why are they not continuing in that treatment?

Patients' medical care is under the direction and responsibility of their own physicians and medical teams outside of the NIH. In deciding whether to seek waivers for PDS products, the PIs have evaluated participant needs and made professional medical determinations of the best course of action for each individual participant. PIs evaluated the risks and potential benefits of seeking waivers for PDS products on a case-by-case basis in consultation with their Institutional Review Boards (IRBs), the FDA, and participants' physicians, as appropriate. Because the studies are ongoing, it would be premature to attempt to draw

conclusions about the results. Many of the protocols are not testing interventions, but are investigating risk factors for disease or the underlying mechanisms of disease progression. In some cases, the PDS product was used to assess physiological function (such as kidney function or neural function). Most of the interventional clinical trials conducted at the Clinical Center are early phase trials and 12 of the 61 protocols were double blind studies, so neither the patients nor the PIs know in which arm of their protocol the patient is enrolled. The goals of these trials are to determine safety, dosage and preliminary data on efficacy.

5. Please list the NIH researchers who sought and got waivers from FDA for their patients.

Studies that had participants scheduled to receive product that got waivers on a case-by-case basis:

- Chen, Alice 13-C-0080
- Dunavin, Neil 15-H-0088
- Gafni, Rachel 07-D-0016
- Hickstein, Dennis 10-C-0174
- Kaler, Stephen 09-CH-0059
- McDermott, David 09-I-0200
- McDermott, David 14-I-0185

6. Please list the NIH researchers who did not seek and get waivers from FDA for their patients.

See #2 for information on protocols that have not sought or received waivers from the FDA.

7. Please list the NIH researchers who sought and got alternative sources of treatment for their patients.

Studies that have obtained and used alternative sources for participants scheduled to receive products since May 22, 2015:

- Bishop, Rachel 08-EI-0169
- Conlon, Kevin 12-C-0113
- Cukras, Catherine 11-EI-0263
- Leggio, Lorenzo 08-AA-0178
- McDermott, David 14-I-0185* (appears on both lists because the protocol got waivers initially and now has an alternative)
- Reich, Daniel 11-N-0116
- Venditti, Charles 04-HG-0127
- Wiley, Henry 12-EI-0042
- Zarate, Carlos 14-M-0085

- 8. Please list the NIH researchers who did not seek and get alternative sources of treatment for their patients.**

See #2 for information on protocols that have not sought or obtained alternative sources.

- 9. Is there anyone at NIH tasked with the responsibility of overseeing the status and care of all the patients in NIH studies disrupted by the PDS issues? If not, why not? If so, who?**

The Clinical Center has been tracking protocols and participants and reporting to the NIH Task Force co-chaired by Drs. Larry Tabak and Kathy Hudson. See #10 for additional information.

- 10. Is the NIH internal task force that is reviewing PDS issues also examining the impacts and status of patients in NIH studies disrupted by the PDS issues? Why or why not?**

Dr. Francis Collins has tasked Dr. John Gallin, Director of the Clinical Center, with ongoing monitoring of protocols and participants affected by the PDS suspension. During the investigation and early response, the NIH Task Force has been responsible for high-level oversight of the protocols and participants affected by the PDS suspension. The Task Force determined appropriate notification strategies as our understanding of the situation evolved and disseminated guidance to investigators. The Task Force also advised the Clinical Center and investigators on seeking waivers and finding alternative sources. The Task Force surveyed investigators to find out which studies had participants scheduled to receive products and determine if there were any studies or participants with needs that were not being addressed through modifications, waivers or alternative sources. These responsibilities are now under the purview of the Clinical Center Director. Clinical decisions for individual participants are under the purview of the principal investigators and participants' medical teams.

November 16, 2015