During the inspection, FDA investigators found an Excel spreadsheet on Semler's server describing the substitution of plasma samples for studies (b)(4). For example, in Study (b)(4), the spreadsheet indicates that plasma samples from subject 10 who received reference product were substituted for the plasma samples from subject 41 who received test product.

OBSERVATION 2
Not all aqueous humor samples were accurately reported in the study report for Study (b)(4). Specifically, the final report states that 19 aqueous humor samples were excluded from the PK analysis because they were contaminated with blood. However, email communications between Semler and the Sponsor in July 2012 documented that only 2 of 19 aqueous humor samples were contaminated.

OBSERVATION 3
During the PK analysis of study (b)(4), the 3.5 hour concentration for subject 21, period 1 was switched with the 3.5 hour concentration for subject 22, period 1 without any documentation of sample mix-up. An investigation undertaken by Semler at the clinical and analytical sites did not uncover any evidence of sample mix-up.

OBSERVATION 4
Not all study-related documentation was retained to allow reconstruction of the study. Specifically,

1. The location of the plasma samples for subjects 17-32, period 1 of study (b)(4) were incorrectly recorded in the freezer log book for freezer 483.

2. The calibrators and QCs used for study (b)(4) could not be reconciled. Based on the log book for freezer 138, 110 set of calibrators were prepared on June 2, 2014 and 25 sets of calibrators remain in the freezer. However, the calibrators and QCs were unable to be located and the freezer log book was not updated.
3. Instrument audit trails were not captured for archived projects performed from January 2015 through May 28, 2015 for chromatographic LC/MS instruments LCMS-138, LCMS-139, and LCMS-475. For example, LCMS 139 instrument was used for analyzing samples from bioequivalence studies without any corresponding audit trail testing information.

4. Not all study-related correspondences were archived with the study file to allow complete reconstruction of study activities.

OBSERVATION 5
Not all raw data were maintained in the study folder. Specifically, bioanalytical data worksheets were discovered crumpled/torn in a trash pile on the floor or otherwise discarded inside the bioanalytical laboratory. Examples include the following:

3. Overview-Area Table Results for Phosphate Analysis study dated September 28, 2015 with the word “Determination” handwritten on the sheet.
5. Results table for study subject 10 dated January 26, 2015.

OBSERVATION 6
Laboratory analysts had the ability to delete, copy and rename chromatographic LC/MS raw data folders and run files on the computer system connected to LC/MS instruments. Specifically,

1. On September 30, 2015, we observed that laboratory analysts could delete data for LCMS 241 instrument that was being used to test samples for bioequivalence studies including:

2. Laboratory analysts had the ability to delete raw data folders and files during the time period of May 28, 2015
and September 9, 2015 on instrument LCMS 139 during the upgrade of Analyst Software System from version 1.4.1 to version 1.6.2. This LCMS 139 instrument was used during this time period to test samples for bioequivalence studies that included (b)(4).

OBSERVATION 7

Not all data generated in the in-vitro bioanalytical laboratory are adequately recorded to prevent accidental data loss. Specifically, the continuous temperature monitoring for the laboratory orbital 37°C shaker (equipment number EOS 799) used for in-vitro bioanalytical testing is recorded on an uncontrolled portable thumb drive. The electronic temperature data that is downloaded on the thumb drive can be deleted/altered.
The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."