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Office of the Provost
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RE: Human Research Subject Protections Under Federalwide Assurance (FWA) -1852 and 5917

Dear Drs. DiNardo and Homan:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the Drexel University (Drexel) on September 13-15, 2010. The evaluation, conducted by two OHRP staff with the assistance of two consultants, included meetings with you, senior institutional officials, institutional review board (IRB) chairpersons, IRB members, the administrative staff of the IRB, and Department of Health and Human Service (HHS) -supported principal investigators who submit protocols to the Drexel IRBs. The evaluation also involved a review of IRB files for approximately 26 open protocols, the review of approximately 20 study amendments, and the minutes of a number of IRB meetings held from 2008 – 2010.

During the OHRP site visit, the IRB chairpersons, members, and administrative staff displayed an enthusiastic and sincere concern for the protection of human subjects. In addition, we noted that investigators recognize the importance of the IRB's role in protecting human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB chairs and staff indicate great dedication to the mission of the IRB. The IRB staff members were enthusiastic about their jobs and their role in the protection of human

subjects. The IRB administrator and staff were very helpful and accommodating to OHRP during the site visit.

Based on the interviews conducted during the on-site evaluation and information reviewed during the evaluation, we make the following determinations:

A. Determinations regarding your institution's system for protecting human subjects

- (1) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research must be reviewed at a convened meeting at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas, and that in order for the research to be approved, it must receive the approval of a majority of those members present at the meeting. HHS regulations at 45 CFR 46.111 require that in order to approve research the IRB must determine that certain requirements are satisfied, including that risks to subjects are minimized; risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

We determine that the Drexel IRBs frequently deferred the approval of studies at convened meetings and requested clarifications or modifications and then approved the research without reviewing those studies at subsequent convened meetings. Furthermore, in several cases, the IRBs had substantive questions and concerns for which the IRBs needed responses from the investigators in order to make the determinations required for approval under HHS regulations under 45 CFR 46.111. Some examples include the following:

- (a) IRB # 18831; Progesterone for the Treatment of Traumatic Brain Injury (ProTECT III); 1RO1 NS062778-01. The study was reviewed at the February 3, 2010 IRB meeting and was deferred to obtain more information about the community consultation. There is no evidence that the study was subsequently approved at a convened meeting of the IRB, but the chair approved the study and notified the principle investigator the study may begin. We further note that the convened IRB would have needed this information in order to determine that the requirements under the "Emergency Research Consent Waiver" were satisfied.
- (b) IRB # 18837; Observation Study of Interferon Alpha Plus Ribarivin Therapy in HCV/HIV-1 Co-Infected and HCV Mono-Infected Subjects. The study was reviewed at the February 3, 2010 IRB meeting and was deferred to obtain more information about what will happen to subjects and what kind of data will be collected and how. There is no evidence that the study was subsequently approved at a convened meeting of the IRB, but the chair approved the study and notified the principle investigator the study may begin. We further note that the convened IRB would have needed this information in order to determine that the

- requirements at 45 CFR 45.111(a)(1) and (2) were satisfied.
- (c) IRB # 18894; A Randomized Clinical Trial of Fetal ECG ST Segment and T Wave Analysis as an Adjunct to Electronic Fetal Heart Rate Monitoring for Prevention of Perinatal Hypoxic-Ischemic Morbidity and Mortality. The study was reviewed at the March 17, 2010 IRB meeting and was deferred to obtain more information about the training of the clinicians involved, about the DSMB, and about the justification for performing the monitoring on subjects with normal or high-risk pregnancies. The study was reviewed again at the April 7, 2010 IRB meeting and was deferred to obtain more information about whether or not subjects in the PILOT study will be randomized and whether or not the data from the PILOT study will be used in the main study. There is no evidence that the study was subsequently approved at a convened meeting of the IRB, but the chair approved the study and notified the principle investigator the study may begin. We further note that the convened IRB would have needed this information in order to determine that the requirements at 45 CFR 45.111(a)(1) and (2) were satisfied.
- (d) IRB # 18895; Antenatal Late Preterm Steroids (ALPS): A Randomized Placebo Controlled Trial; 1U01HL098354-01. The study was reviewed at the March 17, 2010 meeting and was deferred to obtain more information about the consent process, and about the DSMB. There is no evidence that the study was subsequently approved at a convened meeting of the IRB, but the chair approved the study and notified the principle investigator the study may begin. We further note that the convened IRB would have needed this information in order to determine that the requirements at 45 CFR 45.111(a)(1), (2) and (4) were satisfied.
- (e) IRB # 18927; Optical Technologies and Molecular Imaging for Cervical Neoplasia. The study was reviewed at the April 7, 2010 meeting and was deferred to obtain more information about the exact activities to take place at Drexel. There is no evidence that the study was subsequently approved at a convened meeting of the IRB, but the chair approved the study and notified the principle investigator the study may begin. We further note that the convened IRB would have needed this information in order to determine that the requirements at 45 CFR 45.111(a)(1) and (2) were satisfied.
- (f) IRB # 18981; Multidisciplinary Model of Nurse Midwife Psychotherapy For Postpartum Depression; 1R21MH086610-01A1. The study was reviewed at the April 21, 2010 meeting and was deferred to obtain more information about the study staff and their training and the role of the local psychiatrist when a subject is determined to have suicidal or homicidal ideations. The study was reviewed again at the May 19, 2010 meeting and was deferred to obtain more information about the questions posed at the previous meeting that had not been addressed.

There is no evidence that the study was subsequently approved at a convened meeting of the IRB, but the chair approved the study and notified the principle investigator the study may begin. We further note that the convened IRB would have needed this information in order to determine that the requirements at 45 CFR 45.111(a)(1) and (2) were satisfied.

Corrective Action: We acknowledge the statement in your September 17, 2010 letter that the Drexel IRBs have implemented policy changes to require that studies will be tabled until the principal investigator can provide information about factors relating to HHS regulations under 45 CFR 46.111. OHRP recommends that the written procedures indicate specifically that, in cases where the study is tabled because insufficient information is provided for the IRB to make the required determinations under 45 CFR 46.111, the research may not be approved until the IRB has reviewed and approved the research study at a subsequent convened meeting, and that all IRB members be trained about these requirements.

We further acknowledge the statement in your September 17, 2010 letter that the Drexel IRBs have implemented policy changes so that when, at a convened meeting, the IRB reviews and approves the research protocol provided that the principal investigator makes conditional change(s) required by the IRB and/or makes minor changes such as the correction of grammatical or syntax error, the principal investigator will be sent a notice indicating that the research has been reviewed and approved by the IRB, contingent upon the principal investigator making the required changes to the protocol. The notice will make it clear that the investigator may not initiate the research project until an *Approved as Submitted* notice is received for the revised research protocol.

We determine that the corrective actions adequately address the above determination.

(2) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. We determine that, for the July 7, 2010 meeting of the Drexel IRB #1, the IRB did not have a nonscientist present at the meeting.

Corrective Action: We acknowledge the statement in your October 4, 2010 letter that the IRB #1 has re-reviewed and approved the entire agenda from the July 7, 2010 meeting at the September 22, 2010 meeting, which included a nonscientist member. We also acknowledge that Drexel has also added additional nonscientist members to the IRB to serve as alternates and has updated the IRB roster registered with OHRP. We determine that this corrective action adequately addresses the above determination.

We also have the following questions and concerns, and provide some recommendations regarding your institution's human subject protection program:

B. Questions and Concerns

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

[Redacted]

Please provide us with responses to the above questions and concerns by December 7, 2010. Feel free to contact me if you would like guidance in developing a corrective action plan.

C. Recommendations

We make the following recommendations regarding Drexel's human subject protection program:

We recommend that minutes of IRB meetings include a description of members who leave and reenter the room. Also, the minutes tend to be hard to follow, particularly since they include language intended for the letter to the investigator (e.g., at the July 7, 2010 meeting, "The subject protocol was reviewed at the 7/7/1010 meeting of the IRB.") In addition, votes are recorded for various items, such as reports to the committee, but it is not clear what the IRB is voting on or for (e.g., "Vote: Eight (8) recorded in favor, none opposed and no abstentions" with no description of what the motion or action was). We recommend that the minutes be recorded to reflect what discussion occurred at the meeting and that they include a description of the motion for the vote or the action approved. In addition, the expedited review category is seldom noted when reporting expedited approvals. We recommend that you do so.

Medical IRB Guidelines:

- (1) Section 1.7 lists activities that may not be considered as human subjects research. OHRP notes that some of these activities, such as measuring and reporting provider performance data for clinical, practical, or administrative uses to carry out a quality improvement project and publish the results could include human subjects research. We recommend you update the Guidelines accordingly.
- (2) Section 3.1J states that unanticipated adverse events be reported to the IRB. OHRP notes that this is only true of unanticipated adverse events that are also unanticipated problems involving risks to subjects or others (e.g., those that are related or possibly related to the research). We note this goes over and above the regulatory requirements.
- (3) We recommend that section 4.2 include the additional elements of informed consent found at 45 CFR 46.116(b).
- (4) Section 4.1.2 appears to be conflating the concepts of waiver of informed consent with waiver of documentation of informed consent. We recommend you update the Guidelines accordingly.
- (5) Section 7.2.4.b states that use of tissue specimens obtained from a repository may be exempt as long as they are provided without identifiers and there are policies preventing the release of personal information. Note that in order to be exempt under the criteria at 45 CFR 46.101(b)(4), the specimens must be existing at the time the research is proposed

and either publicly available or recorded by the investigator in such a way that subjects cannot be identified. We note that the research described in the Guidelines may not involve human subjects under OHRP's guidance on research involving coded private information or specimens, available at <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>. We recommend you update the Guidelines accordingly.

- (6) Section 7.4.2 appears to conflate the concept of "minimal risk" and the expedited review categories. Please note that in order to be eligible for expedited review, the research must be both minimal risk and appear on the categories of research eligible for expedited review. Also in this section, 9a and b discuss "retrospective" and "prospective" collection of data, documents, etc. Please note that only prospective use of data collected for non-research purposes may be eligible for expedited review. We recommend you update the Guidelines accordingly to clarify that data collected prospectively for research purposes may not be reviewed in an expedited manner.
- (7) Section 7.8 discusses protocols lacking definite plans for human involvement and states that the IRB can approve such studies in an expedited manner. Please note that no IRB review is necessary until plans have been developed in accordance with HHS regulations at 45 CFR 46.118.
- (8) We recommend that section 7.12 on Consent by Telephone be modified to note that this procedure can only be used when the IRB has appropriately waived documentation of informed consent.
- (9) Section 8.1 appears to require reporting of all adverse experiences to IRB. Note that only those that are also unanticipated problems involving risks to subjects or others need to be reported. We recommend you update the Guidelines accordingly.
- (10) Section 9 should be updated to include the most recent version of Subpart B. Also, we suggest that the Reviewer's Checklist for Pregnant Women, Human Fetuses, Neonates or Fetal Material be updated to reflect the most recent version of Subpart B.

IRB Standard Operating Procedures:

- (1) Page 24 and 25, under section 10, appear to state that investigators may obtain clinical information about subjects for the purposes of contacting potential subjects and other "preparatory to research activities" prior to obtaining IRB review and approval of the study. Please note that for HHS-supported non-exempt human subjects research, this would be considered obtaining identifiable private information for research purposes and would require IRB review and approval. We recommend you update the written procedures accordingly.
- (2) We recommend that the list of exemptions on page 36 use the regulatory language found

at 45 CFR 46.101(a).

- (3) For the listing of requirements for waiver of informed consent on page 46, the “and” between section (a) and section (b) should be an “or.”
- (4) Page 47, section 13 states “In multi-site trials, investigators are required to report adverse events that occur in subjects enrolled elsewhere...only when the adverse event is both serious and unexpected.” Please note that all unanticipated problems involving risks to subjects or others need to be reported to the IRB, not just those that are serious. We recommend you update the written procedures accordingly.
- (5) Page 57-59, “Research Directed Toward the Fetus In-Utero” should be updated to include the most recent version of Subpart B.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please feel free to contact me should you have any questions.

Sincerely,

Kristina C. Borrer, Ph.D.
Director
Division of Compliance Oversight

C c: Dr. Sreekant Murthy, Vice Provost for Research Compliance, Drexel
Dr. Abhay J. Dhond, IRB Chairperson, Drexel IRB #1
Dr. Frank Linnehan, IRB Chairperson, Drexel IRB # 3
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Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH