



ORDER TO CEASE MANUFACTURING HCT/PS

November 25, 2019

HAND DELIVERED

Rosa I. Cruz, MD,
Medical Director and Owner
Gynecology, Reproductive Endocrinology and Fertility Institute (GREFI)
1519 Avenue Ponce de Leon
San Juan, PR 00909-1732

Dear Dr. Cruz:

Your establishment, Gynecology, Reproductive Endocrinology and Fertility Institute (GREFI or Establishment), located at 1519 Avenue Ponce de Leon, San Juan, Puerto Rico, performs donor screening, is responsible for donor testing, and determines the eligibility of anonymous and directed donors of reproductive human cells, tissues or cellular or tissue-based products (HCT/PS), and therefore manufactures HCT/PS as defined at 21 CFR 1271.3(d). Your Establishment also performs other manufacturing steps, such as storage. The Food and Drug Administration (FDA or agency) conducted an inspection of your Establishment between August 26 and October 1, 2019, and at the conclusion of the inspection, the FDA investigators issued you¹ a Form FDA-483, List of Inspectional Observations.² Our review of the information and records examined and collected during the inspection revealed significant violations by GREFI of Title 21, Code of Federal Regulations, Part 1271 (21 CFR Part 1271), issued under the authority of Section 361 of the Public Health Service Act (PHS Act) [42 United States Code (USC) 264]. Furthermore, FDA has determined that because your Establishment is in violation of the regulations at 21 CFR Part 1271, your Establishment does not provide adequate protections against the risks of communicable disease transmission. The Agency further concludes that there are reasonable grounds to believe the HCT/PS manufactured by your Establishment pose a danger to health. Accordingly, FDA issues this Order to Cease Manufacturing, effective immediately.

This Order to Cease Manufacturing relates to conduct occurring on or after May 25, 2005, the effective date of the applicable regulations and applies only to HCT/PS from anonymous and directed donors. A donor eligibility determination is not required for reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use.

¹ Throughout this order, “you” refers both to the Establishment, and/or you personally, as well as in your capacity as Medical Director and Owner, as appropriate.

² FDA issued a Form FDA-483 on September 12, 2019, an amended Form FDA-483 on October 1, 2019, and a second amended Form FDA-483 on October 8, 2019.

Pursuant to 21 CFR 1271.440(a)(3), FDA hereby orders you to:³

1. Immediately cease all manufacturing of HCT/Ps from directed or anonymous reproductive tissue donors until compliance with the regulations in 21 CFR Part 1271 has been achieved and you have been provided with written authorization from FDA to resume operations. Under 21 CFR 1271.3(e) manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.
2. Continue to store all HCT/Ps recovered on or after May 25, 2005, which are in your possession or are received after the date of this Order.

Additionally, we request that you immediately notify, by copy of this Order, any persons who since May 25, 2005:

- were recipients of anonymous or directed donations of reproductive tissues (such as gestational carriers or surrogates);
- have offspring as the result of an Assisted Reproductive Technology (ART) cycle with your Establishment, involving an anonymous or directed reproductive tissue donor; or
- have stored tissues that involve anonymous or directed reproductive tissue donors.

We further request that you provide FDA with a copy of the cover letter, if any, you include with the copy of the Order and a list of the individuals you notify.

If you have any clients who, at the time of receipt of this Order, are currently undergoing hormonal stimulation for recovery or implantation of reproductive tissues, please contact Dr. Ping He at 240-402-9327 or Ping.He@fda.hhs.gov.

FDA's inspection and record review noted significant noncompliance with the relevant federal regulations including, but not limited to, the following:

DONOR ELIGIBILITY

1. Failure to use appropriate FDA-licensed, approved, or cleared donor screening tests to test a specimen from an anonymous or directed reproductive donor for evidence of infection due to relevant communicable disease agents, including human immunodeficiency virus, types 1 and 2 (HIV-1/2), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Treponema pallidum* [21 CFR 1271.80(c); 21 CFR 1271.85(a)]. For example:
 - a. Semen was collected from directed donor (b) (6); however, there was no testing for relevant communicable disease agents on any specimen collected from directed donor (b) (6)
 - b. Oocytes were retrieved from directed donor (b) (6),

³ Neither this order, nor the observations listed on the Form FDA-483, are intended to be an all-inclusive list of your violations. FDA reserves the right to seek any and all other actions and remedies relating to the violations described in this order or any other violations.

- (b) (6). A specimen for testing was collected on (b) (6) and tested for HIV, HBV, and HCV; however, there is no evidence that these tests were FDA-licensed, approved, or cleared donor screening tests. No further specimens from directed donor (b) (6) were collected for relevant communicable disease agent testing for purposes of the (b) (6) donations.
- c. Semen was collected from directed donor (b) (6). A specimen for testing was collected on (b) (6) and tested for HIV, HBV, and HCV; however, there is no evidence that these tests were FDA-licensed, approved, or cleared donor screening tests. No further specimens from directed donor (b) (6) were collected for relevant communicable disease agent testing for purposes of the (b) (6) donation.
 - d. Oocytes were retrieved from directed donor (b) (6). A specimen for testing was collected on (b) (6) and tested for HBV and HCV; however, there is no evidence that these tests were FDA-licensed, approved, or cleared donor screening tests.
 - e. Testing for West Nile Virus (WNV) was not performed for anonymous donor (b) (6), directed donor (b) (6), directed donor (b) (6), and directed donor (b) (6)⁴.
 - f. Testing for HIV-1, HBV, or HCV by the nucleic acid test (NAT) method was not performed for anonymous donor (b) (6), directed donor (b) (6), directed donor (b) (6), and directed donor (b) (6).
2. Failure to test a specimen from an anonymous or directed reproductive donor to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents of the genitourinary tract. The reproductive cells or tissue were not recovered by a method that ensured freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract [21 CFR 1271.85(c)]. Specimens from directed donor (b) (6), directed donor (b) (6) and directed donor (b) (6) were not tested for *Chlamydia trachomatis* or *Neisseria gonorrhoea*.
 3. Failure to collect donor specimens for testing at the time of recovery of cells or tissue from the donor; or for oocyte donors, up to 30 days prior to oocyte recovery or up to seven days after recovery; or for semen donors, up to seven days before or after recovery [21 CFR 1271.80(b)]. For example:
 - a. Oocytes were retrieved from directed donor (b) (6). A specimen for testing was collected on (b) (6), however the specimen collection was not within the required timeframe for any of the three donations.
 - b. Semen was collected from directed donor (b) (6). A specimen for testing was collected on (b) (6), however the specimen collection was not within the required timeframe for either donation.

⁴ WNV is a relevant communicable disease agent or disease as defined in 21 CFR 1271.3(r)(2) based on the risk of transmission, severity of effects, and availability of appropriate screening measures. For further discussion, see Guidance for Industry, *Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)* (August 2007) and Guidance for Industry, *Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)* (corrected May 2017).

- c. Oocytes were retrieved from directed donor (b) (6). A specimen for testing was collected on (b) (6), however the specimen collection was not within the required timeframe for this donation.
4. Failure to determine a donor of cells or tissue to be eligible, based upon the results of donor screening in accordance with 21 CFR 1271.75 and donor testing in accordance with 21 CFR 1271.80 and 1271.85, prior to implantation, transplantation, infusion, or transfer of the HCT/P(s) [21 CFR 1271.45(c); 21 CFR 1271.50(a)]. For example, oocytes were recovered from anonymous donor (b) (6). A specimen for relevant communicable disease testing was collected from donor (b) (6) and the results were reported by the testing laboratory on July 20, 2019. However, HCT/Ps from donor (b) (6) were transferred to the recipient on (b) (6), prior to collection of the testing specimen and receipt of testing results, which are required in order to make a donor eligibility determination. Despite the missing test results, donor (b) (6) was determined eligible.
5. Failure to determine as ineligible donors who are identified as having a risk factor for or clinical evidence of any of the relevant communicable disease agents or diseases for which screening is required [21 CFR 1271.75(d)(1)]. For example, the records for anonymous oocyte donor (b) (6) document her residence as Puerto Rico, which is an area considered at increased risk for Zika virus (ZIKV). Donor (b) (6) was determined eligible despite this risk factor for ZIKV.⁵
6. Failure of a responsible person to determine whether a donor is eligible based upon the results of donor screening in accordance with 21 CFR 1271.75 and donor testing in accordance with 21 CFR 1271.80 and 1271.85, and to document the eligibility [21 CFR 1271.50(a)]. For example:
 - a. Records for the following donors did not contain any documentation that the donors were determined eligible, based on the results of donor screening and testing:
 - i. Directed oocyte donor (b) (6) (oocyte recovery dates: (b) (6)). A form in the donor's record, "GREFI PGD Embryology Report," documents "no determination required" for this donor;
 - ii. Directed semen donor (b) (6) (semen recovery dates: (b) (6)). A form in the donor's record, "GREFI PGD Embryology Report," documents "no determination required" for this donor;
 - iii. Directed oocyte donor (b) (6) (oocyte recovery date: (b) (6)) and
 - iv. Directed semen donor (b) (6) (semen recovery date: (b) (6))

⁵ ZIKV is a relevant communicable disease agent or disease as defined in 21 CFR 1271.3(r)(2) based on the risk of transmission, severity of effects, and availability of appropriate screening measures. In general, an area is considered to have an increased risk for ZIKV transmission when locally transmitted, mosquito-borne ZIKV has been reported or the potential is suspected based on epidemiological evidence. Puerto Rico is considered at increased risk for ZIKV based on its prior reports of mosquito-borne ZIKV transmission. For further discussion, see Guidance for Industry, *Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products* (updated May 2018).

- b. Forms documenting eligibility for anonymous oocyte donor (b) (6) were incomplete. The “*Eligibility Determination Form - Summary*” was missing the signature of the responsible person who made the determination and the date of the eligibility determination. The “*DED Checklist*” form did not contain documentation of the date the responsible person made the eligibility determination. Oocytes were recovered from donor (b) (6).
7. Failure to screen a donor of reproductive cells or tissue by reviewing the donor’s relevant medical records for risk factors for, or clinical evidence of, relevant communicable disease agents and diseases [21 CFR 1271.75(a)(1)]. “Relevant medical records” includes, in relevant part, a current donor medical history interview and a current report of the physical examination of a living donor [21 CFR 1271.3(s)]. For example, records for the following donors lack documentation of a donor medical history interview and/or a physical examination:
 - a. Directed oocyte donor (b) (6) (oocyte recovery date: (b) (6))
 - b. Directed semen donor (b) (6) (semen recovery dates: (b) (6)) and
 - c. Directed semen donor (b) (6) (semen recovery date: (b) (6))
8. Failure to establish and maintain procedures for all steps performed in testing, screening, determining donor eligibility, and complying with all other requirements of Subpart C “Donor Eligibility” in 21 CFR Part 1271 (21 CFR 1271.45-1271.90). “Establish and maintain” means define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis [21 CFR 1271.47(a)]. For example, your procedures are missing requirements for testing, screening, and donor eligibility determinations, to include but not limited to, testing for HIV-1/HBV/HCV NAT and WNV. We note that this was brought to your attention during a prior inspection and was not corrected.
9. Failure to ensure, before entering into a contract, agreement, or other arrangement with another establishment to perform any step in manufacture for you, that the establishment complies with applicable current good tissue practice (CGTP) requirements [21 CFR 1271.150(c)(1)(iii)]. For example, there is no documentation to support that several of the testing laboratories you engage to test donors for relevant communicable diseases are using FDA-licensed, approved, or cleared donor screening tests.

ADDITIONAL COMMENTS

Following the receipt of FDA’s October 9, 2018 Untitled Letter, you made revisions to your procedure, “*Human Cells, Tissue, and Cellular and Tissue-Based Products (HCT/Ps) Policy*” (date implemented: November 9, 2018). However, we continue to have concerns about this procedure manual, as set forth below. Please note that this list is not necessarily all-inclusive. It continues to be your responsibility to ensure full compliance with 21 CFR Part 1271.

1. The “Donor Screening” section of your procedure manual states for anonymous donors that, “Repeat donors must undergo full screening and testing at least every 6 months.” This is not correct for repeat anonymous oocyte donors. For repeat anonymous oocyte donors, you must collect a donor specimen for testing at the time of recovery of cells or tissue from the donor or up to 30 days before or up to seven days after recovery, in accordance with 21 CFR 1271.80(b).

2. In the “Donor Screening” section, under anonymous donors, the WNV section does not include risk factors regarding a medical diagnosis or suspicion of WNV infection.
3. In the “Donor Screening” section, under anonymous donors, the ZIKA virus section includes only one risk factor related to donors who test positive for ZIKA virus infection, which is not adequate to assess ZIKV risk. Please note that currently available tests for ZIKV are not considered appropriate for preventing transmission of ZIKV through HCT/Ps. Your procedure does not include any of the following risk factors:
 - a. Medical diagnosis of ZIKV in the past 6 months;
 - b. Residence in, or travel to, an area with an increased risk for ZIKV transmission within the past 6 months; or
 - c. Sex within the past 6 months with a person who has either of the risk factors listed in the two items above.
4. In the section titled, “CJD or vCJD infection,” for anonymous and directed donors, the fifth bulleted item that states, “is a current or former U.S. military member, civilian military employee...” does not specify that the relevant 6-month periods are determined on a cumulative basis (i.e., “...for 6 months or more cumulatively from 1980 through 1990” and “...for 6 months or more cumulatively from 1980 through 1996”).
5. In the section titled, “CJD or vCJD infection,” for anonymous and directed donors, the second bulleted item from the bottom states, “received any transfusion of blood or blood components in the U.K. between 1980 and the present”; however, receipt of such transfusions in France is not included as a risk factor.
6. The “Donor Screening” section, under directed donors, does not include any risk factors for WNV and ZIKV.
7. The “Donor Screening” section under “Directed Donor,” lists factors to look for during review of a donor’s relevant medical records. The procedure states for infection with HIV, hepatitis, syphilis, vaccinia, sepsis, HTLV, and CJD/vCJD that, “A finding of any of the following would require special labeling of HCT/P.” However, you must also determine a donor to be ineligible when donor screening indicates risk factors for, or clinical evidence of, any of the relevant communicable disease agents or diseases for which screening is required [21 CFR 1271.75(d)(1)].
8. In the “Donor Testing” section for anonymous donors, your procedure requires testing for HBsAg, anti-HBc-IgG, and anti-HBc-IgM and states, “A positive test to HBsAg may not make the donor ineligible.” However, under 21 CFR 1271.80(d)(1), a donor whose specimen tests reactive on a screening test for a communicable disease agent in accordance with 21 CFR 1271.85 must be determined to be ineligible (except for a donor whose specimen tests reactive on a non-treponemal screening test for syphilis and negative on a specific treponemal confirmatory test). This applies to both anonymous and directed donors.
9. The “Donor Testing” section states for directed donors that positive results for certain of the listed tests “would require special labeling of HCT/P.” However, we note that your procedure

does not specify that directed donors with positive test results for a relevant communicable disease agent be determined ineligible in accordance with 21 CFR 1271.80(d).

10. We note that your “*Donor Medical History Interview Form*” attached to the back of the procedure manual was also revised on November 9, 2018. However, our review of the form noted the following:
- a. Question #13 regarding a medical diagnosis of WNV infection states, “If the answer is yes to this question defer donation for 28 days from onset of symptoms or 14 days after condition has resolved whichever is the later date.” However, persons who have had a medical diagnosis or suspicion of WNV infection should be deferred for 120 days following diagnosis or onset of illness, whichever is later. (See Guidance for Industry, *Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*, section IV.E).
 - b. The form does not include a question regarding suspicion of WNV infection or persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days.
 - c. The form does not include a question regarding persons who have been treated for or had syphilis within the preceding 12 months.
 - d. Question #25 regarding risks of variant Creutzfeldt-Jakob Disease (vCJD) for persons who lived on military bases does not specify that the relevant 6-month periods are determined on a cumulative basis.
 - e. The form does not include a question regarding receipt of any transfusion of blood or blood components in France between 1980 and the present.
 - f. The form does not include a question regarding sex within the past 6 months with a person who had a medical diagnosis of ZIKV in the past 6 months or who resided or traveled to an area with an increased risk for ZIKV transmission within the past 6 months.
11. We note that your “*Donor Testing Form*” attached to the back of the procedure manual was also revised on November 9, 2018. However, our review of the form noted that it still does not include HBV NAT. In addition, you have listed Zika Virus testing on the form. We note that there are currently no available tests for ZIKV that are considered appropriate for preventing transmission of ZIKV through HCT/Ps.

We note that we have similar concerns regarding your “*Donor Medical History Interview Form*” (created January 26, 2017). For example, the questions regarding ZIKV risk factors do not capture residence in, or travel to, all areas with an increased risk of ZIKV transmission. And Question #32 asks about sex with a male—rather than with any person—who has been diagnosed with ZIKV in the past 6 months or who has traveled to certain areas in the past 6 months. Also, Question #26 regarding risks of variant Creutzfeldt-Jakob Disease (vCJD) for persons who lived on military bases does not specify that the relevant 6-month periods are determined on a cumulative basis. Although it appears you have an updated version of this form

(revised on November 9, 2018), the January 2017 version was used in 2019 for anonymous oocyte donor (b) (6).

This letter confirms the telephone conversation on November 25, 2019, in which notice was given that, pursuant to 21 CFR 1271.440(a)(3), you must:

1. Immediately cease all manufacturing of HCT/Ps from directed or anonymous reproductive tissue donors until compliance with the regulations in 21 CFR Part 1271 has been achieved and you have been provided written authorization from FDA to resume operations. Under 21 CFR 1271.3(e), manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor; and
2. Continue to store all HCT/Ps recovered on or after May 25, 2005, which are in your possession, or received after the date of this Order.

Neither you, nor your Establishment, can resume operations without prior written authorization from FDA. Before FDA will issue such an authorization, you must ensure compliance with FDA's regulations in 21 CFR Part 1271 – including, but not limited to, the Donor Eligibility requirements in 21 CFR Part 1271, Subpart C. Any continued manufacturing of HCT/Ps in violation of this Order constitutes a violation of Section 368 of the PHS Act [42 USC 271], for which criminal penalties may be imposed. FDA retains authority to pursue other actions and remedies.

Within five (5) working days from the receipt of this Order to Cease Manufacturing, you may request a hearing on the matter in accordance with 21 CFR Part 16 (copy attached), to Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., WO71-G112, Silver Spring, MD 20993-0002 (telephone: 240-402-9153). Should you need additional time in which to request a hearing, please notify us immediately, in writing, of your request for additional time.

Failure to request a hearing within the specified time period constitutes a waiver of the right to a hearing. You may also wish to inform yourself with respect to the agency's guidelines regarding electronic media coverage of its administrative proceedings, which can be found at 21 CFR Part 10, Subpart C.

Sincerely,

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

Effective Date: _____ Time: _____

Attachments (2)
21 CFR Part 1271
21 CFR Part 16