Exemptions and Alternatives to the Donor Eligibility Regulations for Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps)

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October 1, 2020

Overview

- Exceptions to the 21 CFR 1271 regulations
  - Limited uses of an HCT/P from an ineligible donor (§ 1271.65(b))
  - Donor Eligibility (DE) determination not required (§ 1271.90(a))
  - Final Rule Related to Reproductive HCT/Ps (§ 1271.90(b))
- Exemptions and Alternatives
- Inquiries & Responses
- Case Scenarios

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Exceptions to Donor Eligibility Regulations for HCT/Ps

DE Determination: Donors That Are Ineligible vs. Not Complete

- Exceptions for use of HCT/Ps from donors with a DE determination that is not complete do not apply to reproductive HCT/P donors
- In order to use an HCT/P from an ineligible donor under the exception in § 1271.65(b), the DE determination must be complete (i.e., based on the results of required testing and/or screening)
- All potential relevant communicable disease agent and disease (RCDAD) risks must be identified in order to comply with labeling and physician notification requirements in § 1271.65(b)(2)-(3)

Limited Use of HCT/P From Ineligible Donor

(§ 1271.65(b))

1. Implantation, transplantation, infusion, or transfer of an HCT/P from an ineligible donor is not prohibited under the following conditions:

   i. Allogeneic use in a first-degree or second-degree blood relative

   ii. Reproductive cells or tissue from a directed reproductive donor (defined under § 1271.3(l))

   iii. Documented urgent medical need (defined under § 1271.3(u))

2. **Special labeling & notification requirements apply (§ 1271.65(b)(2)-(3))**

3. **Document that you notified physician of results of RCDAD testing and screening**

DE Determination Not Required

(§ 1271.90(a))

1. Cells and tissues for autologous use
2. Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use
3. Cryopreserved cells or tissues for reproductive use, other than embryos, originally excepted under (a)(1) or (a)(2) at time of donation that are subsequently intended for directed donation, provided that:
   i. additional donations are unavailable (e.g., due to infertility or health condition of the donor), and
   ii. appropriate measures are taken to screen and test the donor(s) before transfer to the recipient
4. Cryopreserved embryos originally excepted under paragraph (a)(2) of this section at the time of cryopreservation, that is subsequently intended for directed or anonymous donation
   - When possible appropriate measures should be taken to screen and test the semen and oocyte donors before transfer of the embryos to the recipient.

Exceptions for Embryos

(§ 1271.90(b))

Revisions to Exceptions Applicable to Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (published June 22, 2016)

- Effective August 22, 2016
- § 1271.90(b): An embryo originally intended for reproductive use for a specific individual or couple that is subsequently intended for directed or anonymous donation for reproductive use is excepted from the prohibition on use under § 1271.45(c) **even when the applicable donor eligibility requirements under subpart C of this part are not met**
- This final rule does not create an exception for deficiencies that occurred in making the donor eligibility determination for gamete donors as required under § 1271.45(b), or for deficiencies in performing donor screening or testing, as required under §§ 1271.75, 1271.80, and 1271.85
- No exemption request is needed when DE regulatory requirements for embryos are not met

Exceptions for Reproductive Use:

(§§ 1271.90(b), 1271.90(c))

- Establishments remain responsible for making the appropriate donor eligibility determination in accordance with part 1271 regulations
- The embryos must be labeled in accordance with § 1271.90(c)
  - Labeling ensures physicians have specific and accurate information to provide to recipients for use in making informed medical decisions
- Examples of when the following warning statements are required:
  - "FOR AUTOLOGOUS USE ONLY,"
  - "NOT EVALUATED FOR INFECTIOUS SUBSTANCES,"
  - "WARNING: Advise recipient of communicable disease risks,"
  - Biohazard legend,
  - "WARNING: Reactive test results for (name of disease agent or disease),"
  - "Advise recipient that screening and testing of the donor(s) were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently."

What Does Embryo Exception Mean?

(§ 1271.90(b), 81 FR 40512)

- FDA is providing greater accommodation of individuals and couples wanting access to embryos originally intended for reproductive use, while continuing to emphasize the applicability of the donor eligibility screening and testing requirements for individual gamete donors
- When an establishment fails to comply with applicable donor eligibility requirements under part 1271 subpart C, the establishment would not be prohibited from making available such embryos for reproductive use in accordance with § 1271.90(b)
  - However, reproductive HCT/P establishments are still required to follow the donor eligibility rule (21 CFR part 1271 subpart C) and must screen and test the gamete donors in accordance with applicable regulations

Exceptions for Embryos
(§1271.90(b))

Embryos formed and cryopreserved on or after May 25, 2005 can be made available for reproductive use if exception under the § 1271.90(b) provision is met

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Exemptions and Alternatives

Exemptions and Alternatives

- § 1271.155(a) You may request an exemption from or alternative to any requirement in subpart C (donor eligibility) or D (Current Good Tissue Practice)
- § 1271.155(b) Request for exemption or alternative. The request must be accompanied by supporting documentation, including all relevant valid scientific data, and must contain either:

  (1) Information justifying the requested exemption from the requirement, or

  (2) A description of a proposed alternative method of meeting the requirement
- § 1271.155(c) Criteria for granting an exemption or alternative if such action is consistent with the goals of protecting the public health and/or preventing the introduction, transmission, or spread of communicable diseases and that:

  (1) The information submitted justifies an exemption; or

  (2) The proposed alternative satisfies the purpose of the requirement.

Exemptions and Alternatives (Continued)

The documentation and scientific data submitted in support of the request must show that the risk of transmission of the RCDAD from the donor to recipient has been mitigated or justified.

For example, if the establishment did not ask the donor whether, in the previous 6 months relevant to the date of gamete recovery, she/he had a medical diagnosis of Zika virus, or resided in, or traveled to, an area with an increased risk for Zika virus transmission, or had sex with a person who has either of these risks, the establishment should follow up with the donor and complete the questionnaire to mitigate the risk.

Exemption Request

Please include the following information with the exemption request:

- Letter summarizing the reason for submitting your exemption
- FDA Establishment Identifier (FEI) number
- Relationship of gamete donor to recipient: anonymous, directed, sexually intimate partner
- Date of recovery/donation of gamete(s)
- Documentation of the DE determination
- Relevant medical records used for donor screening (see § 1271.75) relevant to the recovery/donation date for:
  - Donor medical history interview
  - Physical examination
  - Other available information

Exemption Request (continued)

Please include the following information with the exemption request:

- Donor testing (see §§ 1271.80, 1271.85):
  - List of FDA-licensed, approved, or cleared donor screening tests that were used for donor testing, and include the tradename of each test and the manufacturer of each test;
  - Name of the laboratory(ies) that performed donor testing, and a copy of the CLIA certificate for each testing laboratory;

Exemption Request (Continued)

Please include the following information with the exemption request:

- Donor testing (see §§ 1271.80, 1271.85):
  - The test result report forms from the testing laboratory(ies) that provide the date(s) of donor specimen collection and all donor testing performed for:
    - Anti-HIV-1/2, HBsAg, anti-HBc (total), anti-HCV, HIV-1 NAT, HBV NAT, HCV NAT, WNV NAT (when applicable), *Treponema pallidum* (syphilis);
    - Anti-CMV (total) and anti-HTLV I/II (for donors of viable, leukocyte-rich cells or tissues);
    - *Chlamydia trachomatis* NAT and *Neisseria gonorrhoeae* NAT (for donors of reproductive cells or tissues). If this testing was not performed, include the description of the method used for recovery of the reproductive cells or tissues.

Exemption and Alternatives

Requests for exemption or alternative should be submitted by mail or email to:

- Director, Office of Tissues and Advanced Therapies
  Center for Biologics Evaluation and Research
  Food and Drug Administration
  10903 New Hampshire Ave
  Document Control Center
  WO71-G112
  Silver Spring, MD 20993-0002

  or
- HCTPExemptions@fda.hhs.gov

Operation under exemption or alternative. You must not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted.

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Inquires From HCT/P Establishments

Syphilis Confirmatory Testing

Q: My laboratory uses an FDA-cleared screening test to test donors for evidence of syphilis. Which tests are acceptable to use as a confirmatory test?

Syphilis Confirmatory Testing (Continued)

A: Per § 1271.80(d)(1), a donor that tests positive on a donor screening assay is considered ineligible, with the exception of "a donor whose specimen tests reactive on a nontreponemal screening test for syphilis and negative on a specific treponemal confirmatory test".

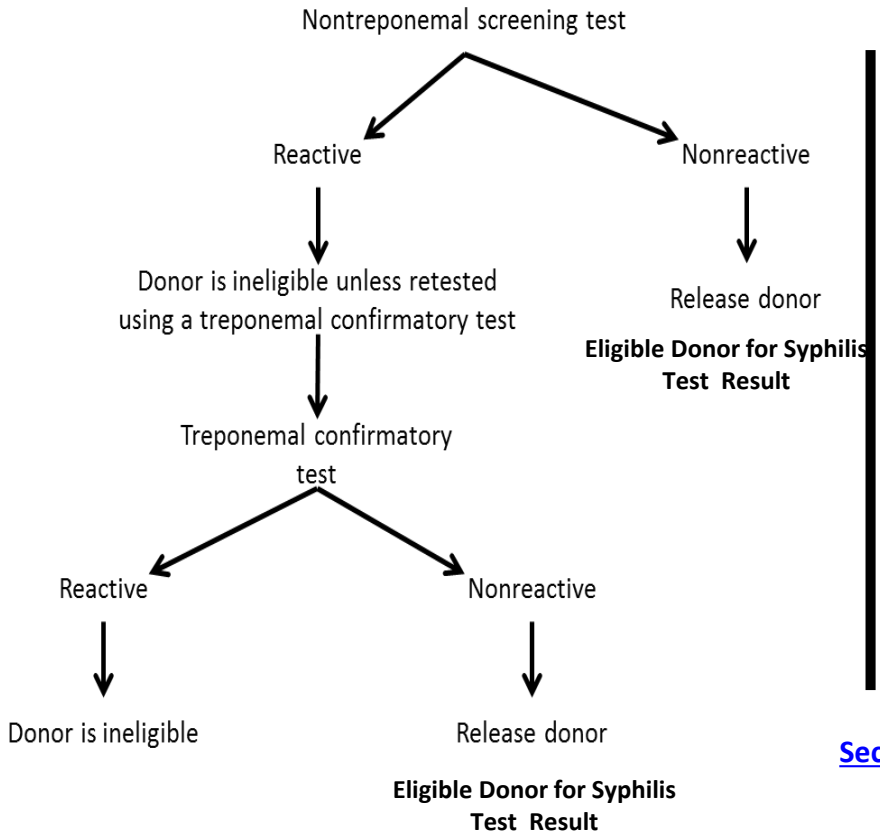
- A "specific treponemal confirmatory test" may include any legally marketed treponemal-specific test, including those that do not have specific "confirmatory" labeling.
- FDA website contains a list of some but not all acceptable *T. pallidum* confirmatory tests. Examples of acceptable Treponemal specific tests are:

  T. pallidum hemagglutination assays (TPHA), *T. pallidum* enzyme linked immunoassays (EIA), *T. pallidum* micro-hemagglutination assay

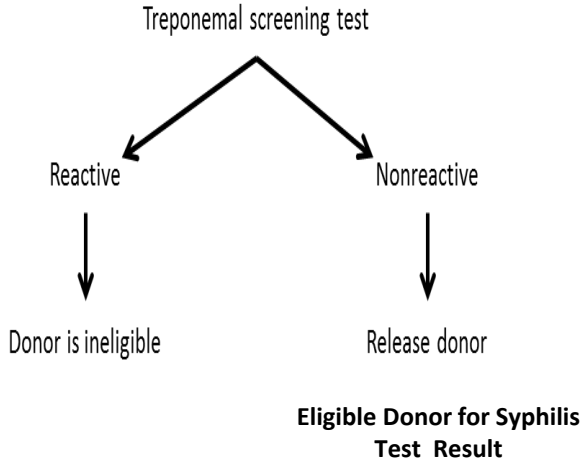
Guidance for Industry: Eligibility Determination for Donors of HCT/Ps, August 2007, Section VI.A.
Guidance for Industry: Use of Donor Screening Tests to Test Donors of HCT/Ps for Infection with Treponema pallidum (Syphilis), September 2015
Donor screening tests at:
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm#syp

Syphilis Confirmatory Testing (Continued)

Traditional Algorithm



Reverse Sequence Algorithm



Section VI.A. of the DE Guidance contains additional useful information regarding syphilis tests.

Cleared Donor Screening Tests – Syphilis

Specific Treponemal Confirmatory and Non-treponemal Screening Assays (Detects antibodies to *T. pallidum* and other serological tests)

Tradename	Infectious Agent	Format	Specimen	Use	Manufacturer	Clearance Date	STN
PK7400 TP HA	*T. pallidum*	Hemagglutination (Treponemal)	*Living:* Serum, Plasma	Donor Screening: detection of IgG and IgM antibodies to *T. pallidum*	Newmarket Biomedical, Ltd. Kentford, Suffolk, UK	8/1/2019	BK180301
ASiManager-AT™	*T. pallidum*	RPR (Non-treponemal)	*Living:* Serum, Plasma *Cadaveric:* Serum, Plasma	Donor Screening: Qualitative detection of reagin antibodies	Arlington Scientific, Inc. Springville, UT	2/19/2015	BK140192
TPHA Screen	*T. pallidum*	Hemagglutination (Treponemal)	*Living:* Serum, Plasma	Donor Screening: Qualitative detection of IgG and IgM antibodies to *T. pallidum*	Immucor, Inc Norcross, GA	10/24/2012	BK120021
Olympus PK TP System	*T. pallidum*	Micro-hemagglutination (Treponemal)	*Living:* Serum, Plasma	Donor Screening: Qualitative detection of IgG and IgM antibodies to *T. pallidum*	Fujirebio Diagnostics Inc. Malvern, PA	2/21/2003	BK030007
ASI TPHA Test	*T. pallidum*	Micro-hemagglutination (Treponemal)	*Living:* Serum	Donor Screening: Qualitative detection of IgG and IgM antibodies to *T. pallidum*	Arlington Scientific, Inc Springville, UT	1/30/2003	BK020031
CAPTIA Syphilis (T. Pallidum)-G	*T. pallidum*	EIA (Treponemal)	*Living:* Serum, Plasma	Donor Screening: Qualitative detection of IgG antibodies to *T. pallidum*	Trinity Biotech Wicklow, Ireland	01/24/2002	K014233

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm#syp

COVID-19 Screening and Testing for Reproductive Donors

Q: Is screening or testing for Covid-19 required for potential donors of reproductive tissue (oocytes and sperm)?

A: FDA has published a safety communication for COVID-19 for HCT/P establishments

- The most recent communication titled "Updated Information for Human Cell, Tissue, or Cellular or Tissue-based Product (HCT/P) Establishments Regarding the COVID-19 Pandemic" was published on July 2, 2020*
- While respiratory viruses, in general, are not known to be transmitted by implantation, transplantation, infusion, or transfer of HCT/Ps, the potential for transmission of COVID-19 by HCT/Ps is unknown at this time

*https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-human-cell-tissue-or-cellular-or-tissue-based-product-hctp-establishments

COVID-19 Screening and Testing for Reproductive Donors (Continued)

A:

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has not been identified by the FDA as a relevant communicable disease agent or disease (RCDAD) under § 1271.3(r)(2) for HCT/Ps. If this changes, industry will be notified through publication of an FDA guidance document.
- Routine screening measures are already in place for evaluating clinical evidence of infection in HCT/P donors. FDA does not recommend using laboratory tests to screen asymptomatic HCT/P donors.

*https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-human-cell-tissue-or-cellular-or-tissue-based-product-hctp-establishments

COVID-19 Screening and Testing for Reproductive Donors (Continued)

A:

- FDA is aware that some HCT/P establishments in the U.S. are considering additional donor screening and testing measures in response to the COVID-19 pandemic

- The HCT/P establishment's responsible person must determine and document the eligibility of a cell or tissue donor (21 CFR 1271.50)

COVID-19 Screening and Testing for Reproductive Donors (Continued)

A: Based on information available at this time, establishments may wish to consider, whether, in the 28 days prior to HCT/P recovery, the donor:

- cared for, lived with, or otherwise had close contact with individuals diagnosed with or suspected of having COVID-19 infection; or
- had been diagnosed with or suspected of having COVID-19 infection; or
- had a positive diagnostic test (e.g., nasopharyngeal swab) for SARS-CoV-2 but never developed symptoms.

FDA will continue to monitor the situation and will issue updates as information becomes available.

TSE Risks - Vegetarian

Q: A donor lived in the U.K. from 1993-1995 but reports that she never ate beef while there because she is a vegetarian. Is her residence in the U.K. considered a TSE risk factor even though she didn't eat meat?

A: Yes. As explained in the 2007 DE guidance, spending 3 months or more cumulatively in the U.K. between 1980 through 1996 is identified as a risk factor for TSE. The guidance does not address specific behaviors associated with a TSE risk. Residence in a country identified in the DE guidance during the timeframes specified is considered a TSE risk factor regardless of specific behaviors reported during that time.

Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 2007, Section IV.E.23.

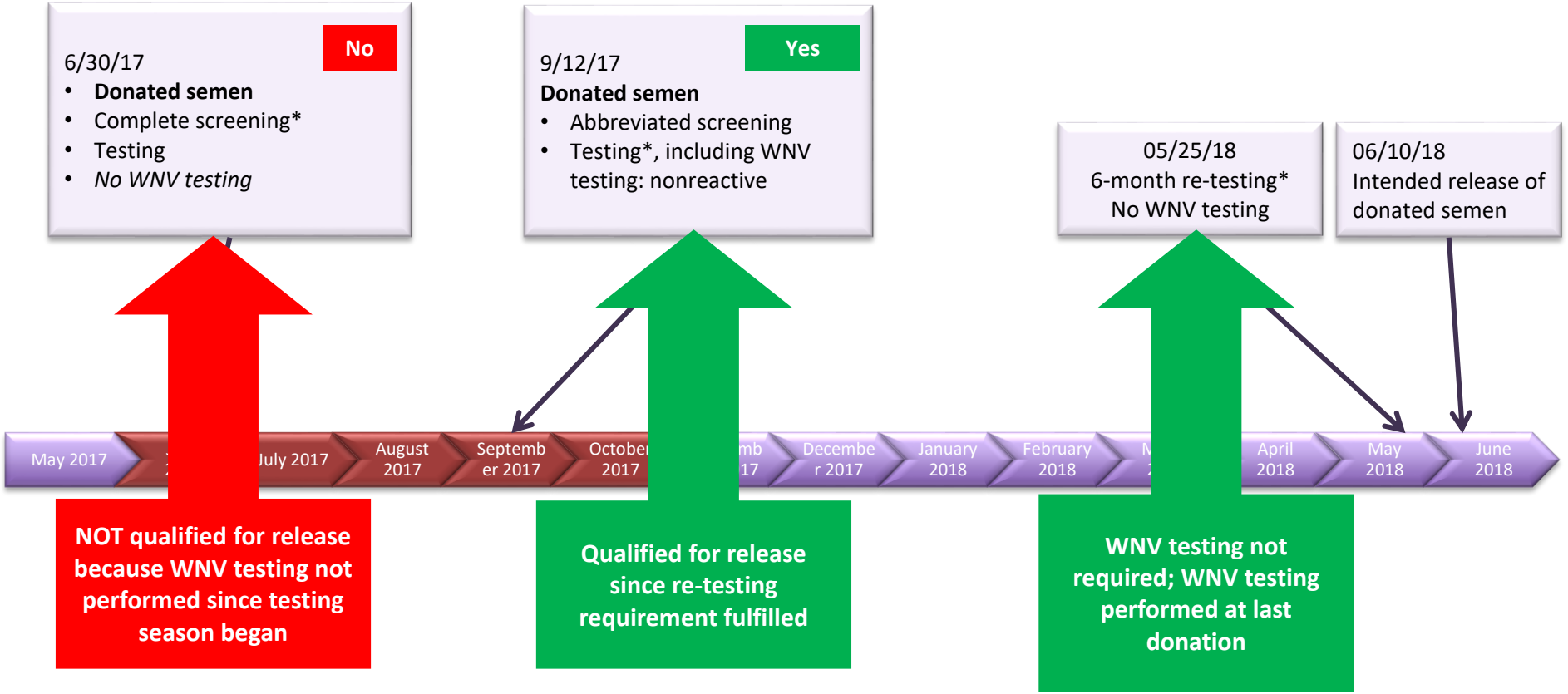
WNV Testing Window

Q: Regarding WNV testing, if for some reason WNV testing is not performed within the June 1st -Oct 31st window for semen donation but all other required testing/screening is performed through the period of donation and the 6 month quarantine period, can all other donations during Nov 1st- May 31st still be accepted? E.g. If testing is performed in August 2018 but is missing WNV testing, is it okay to keep donations starting Nov 1, 2018?

A: Yes, for HCT/Ps recovered November 1st - May 31st , WNV NAT testing is not required for establishments located within the US. Please note that donor screening for WNV risk is required year-round for establishments located outside of the US. In the scenario described, donor testing occurred in August without WNV NAT, which would make the donor eligibility determination not complete. For the semen donated starting November 1, 2018, if all other donor screening and donor testing requirements have been fulfilled, the semen donation from November 1st – May 31st may be released for use without WNV NAT results.

Q&A #1

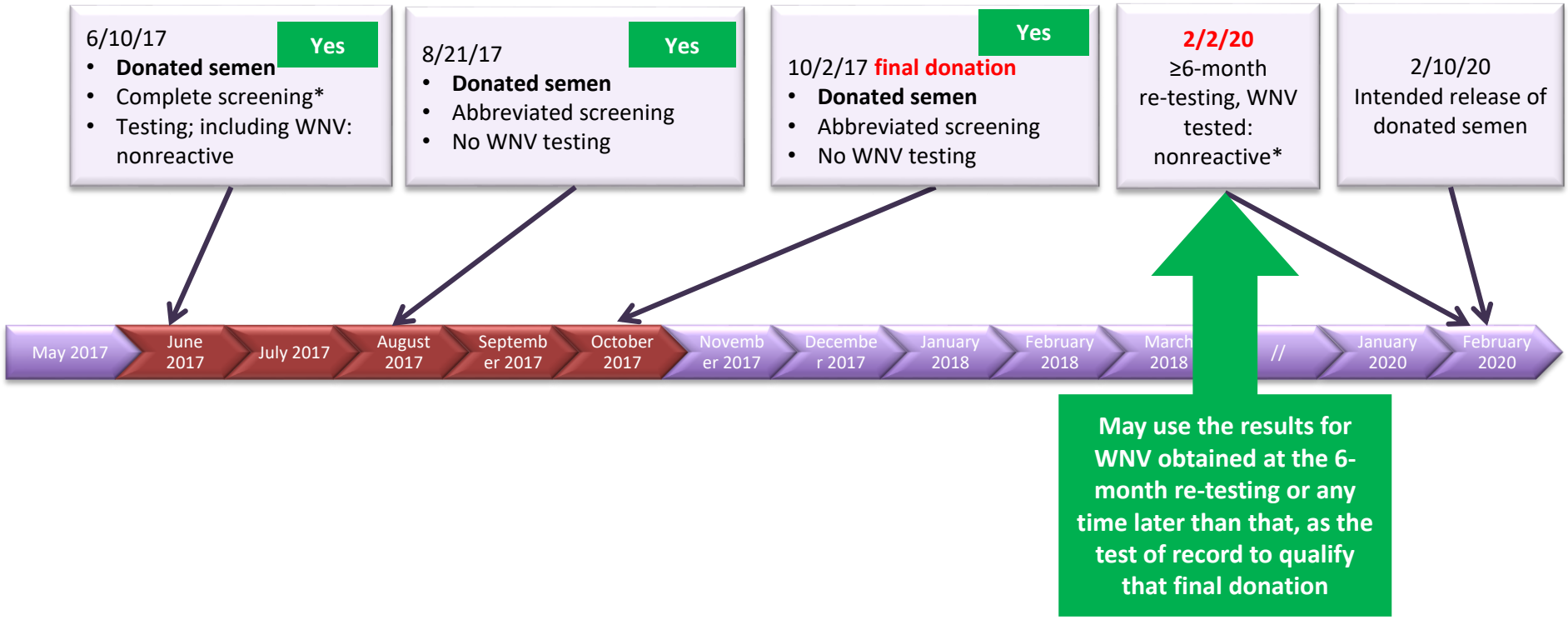
Q: What if WNV testing was not performed for the first donation for the repeat anonymous semen donor? Which donations qualify for release?



* Assumes all applicable requirements/recommendations were followed, and no risks were identified. 6 month quarantine and re-testing requirements apply.

Q&A #2

Q: What if WNV testing was not performed for the final donation for the repeat anonymous semen donor? Which donations qualify for release?



* Assumes all applicable requirements/recommendations were followed, and no risks were identified. 6 month quarantine and re-testing requirements apply.

Area with Increased Risk for ZIKV Transmission

Q: If an anonymous oocyte donor traveled to an area with an increased risk for ZIKV transmission within the past 6 months and is determined to be ineligible, is there an option to document a "departure from protocol" and allow her to donate as long as she waited the CDC's recommended amount of time after returning from travel?

A: No. The § 1271.47(d) regulation pertaining to departure from procedures would not be applicable to this scenario. The May 2018 "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" indicates that an anonymous oocyte donor who traveled to an area with an increased risk for ZIKV transmission within the past 6 months should be considered ineligible. Under §§ 1271.75(d), an anonymous reproductive donor who has been determined ineligible would not be eligible to donate.

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, May 2018

Directed Donors with Risk Factors for ZIKV

Q: What is the recommendation for known or directed donors in regards to Zika?

A: The recommendation in the May 2018 Zika Guidance states living donors of HCT/Ps should be considered ineligible if they have any of the following risk factors:

1. Medical diagnosis of ZIKV in the past 6 months.
2. Residence in, or travel to, an area with an increased risk for ZIKV transmission within the past 6 months.
3. Sex within the past 6 months with a person who has either of the risk factors listed in items 1 or 2, above.

The above recommendations apply to all living donors of HCT/Ps, including directed living donors of HCT/Ps.

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, May 2018

Directed Donors with Risk for ZIKV (Continued)

A: According to § 1271.65(b)(1)(ii), use of an HCT/P from an ineligible donor is not prohibited, if the HCT/P consists of reproductive cells or tissue from a directed reproductive donor, as defined in § 1271.3(l). However, an anonymous reproductive donor who has been determined ineligible would not be eligible to donate in accordance with applicable regulations (§§ 1271.75(d)).

Directed Donor with Risk Factors for ZIKV (Continued)

A: As described in § 1271.3(l), a directed reproductive donor means a donor of reproductive cells or tissue (including semen, oocytes, and embryos) to which the donor contributed the reproductive tissue to a specific recipient, and who knows and is known by the recipient before donation.

Directed Donors with Risk Factors for ZIKV (Continued)

A: For an HCT/P from an ineligible directed donor of reproductive cells or tissue to be made available for limited use under § 1271.65(b), the regulatory requirements include:

- all required donor testing and screening are complete in accordance with 21 CFR part 1271 regulatory requirements,
- a donor eligibility determination has been made in accordance with §§ 1271.45(b) and 1271.65(b),
- tissues are properly labeled as described in § 1271.65(b) with the intention being that the recipient is informed of the potential communicable disease risks, and
- documentation that you notified the physician using the HCT/P of testing and screening results as described in § 1271.65(b). Special labeling requirements apply.

ZIKV Testing

Q: I have a living donor who recently traveled to a country with increased risk for ZIKV transmission. If I test the donor for evidence of ZIKV and the results are negative, can the donor be considered eligible provided that HCT/P labeling indicates the type of test that was used?

A: No. Although nucleic acid tests (NATs) for donor screening are available, they are not considered appropriate for preventing transmission of ZIKV through HCT/Ps. ZIKV is known to persist in certain cells and tissues (e.g., semen, gestational tissues) longer than in blood plasma, so a nonreactive blood plasma NAT does not assure that recovered cells and tissues are not infected with ZIKV. If a test result is negative or nonreactive it does not override any risk factors identified in the HCT/P ZIKV guidance updated in May 2018, and a donor who has a reactive or positive ZIKV test result is considered ineligible even if no other risk factors are identified.

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, May 2018

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Case Scenarios

Case #1

- A 26 year old female is requesting to become an anonymous oocyte donor. She had previously requested to become an oocyte donor 18 months prior and was denied.

- A reactive RPR result and a reactive FTA-ABS result dated 18 months prior is documented in the patient's chart. It is documented that the patient underwent successful treatment for syphilis at that time.

- Her current RPR result is non-reactive. All other donor screening questions and donor tests of record were performed in accordance with 1271 regulations and were also negative.

Case #1 (Continued)

- **Is the donor eligible?**
  - Under § 1271.80(d)(1), the donor may be eligible.

- **Is an exemption request needed?**
  - An exemption request is not needed.

Case #2

- A 35 year old male would like to be a directed semen donor for his brother. The recipient is the brother's wife.

- All donor screening questions and donor tests of record were performed in accordance with 1271 regulations and were negative.

- Over a four week period, three semen samples were collected and frozen. The samples were quarantined for 6 months from the date of the final collection and the donor was retested after 6 months.

- Hepatitis B core Antibody was positive. All other donor screening questions and donor tests of record are negative.

Case #2 (Continued)

- **Is the donor eligible?**
  - No. The donor would have to be determined to be ineligible.
- **Can the HCT/P from a directed reproductive donor (§ 1271.3(l)) be used?**
  - Under §1271.65(b)(ii), the HCT/P is not prohibited from being used.
  - The HCT/P must be labeled prominently with the Biohazard legend and with the statements "WARNING: Advise patient of communicable disease risk," and "WARNING: Reactive tests results for Hepatitis B core antibody"
- **Is an exemption request needed?**
  - No, provided donor eligibility is completed according to 1271 regulations

Contact Information

- **Ping He, M.D.**

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  Simone.porter@fda.hhs.gov
- **Regulatory Questions:**

  OTAT Main Line: 240-402-8190

  Email: OTATRPMS@fda.hhs.gov
- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **CBER Phone:** 1-800-835-4709 or 240-402-8010
- **CBER Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**:

  industry.biologics@fda.hhs.gov
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