OVERVIEW OF HCT/P DONOR ELIGIBILITY

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Objectives

- What is a donor eligibility determination, and when is it required?
- What are the donor screening requirements?
- What are the donor testing requirements?
- What are the exceptions to the rule?
- Additional information about Zika virus

★ This presentation does not include a complete listing of regulatory requirements. Please refer to 21 CFR part 1271 for a complete listing.
WHAT IS A DONOR ELIGIBILITY DETERMINATION, AND WHEN IS IT REQUIRED?
# 21 CFR Part 1271

- **Effective May 25, 2005**

<table>
<thead>
<tr>
<th>21 CFR Part 1271</th>
<th>Issues Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpart A: General Provisions</td>
<td>Definitions, criteria for regulatory pathways determination (e.g. 361 tissue vs. 351 biologic)</td>
</tr>
<tr>
<td>Subpart B: Establishment Registration and Listing</td>
<td>Applicability: types and uses of products that will be regulated by these rules, requirements for registering and listing establishments/products</td>
</tr>
<tr>
<td><strong>Subpart C: Donor Eligibility Determination</strong></td>
<td>Requirements for donor screening and testing for “relevant communicable disease agents and diseases”</td>
</tr>
<tr>
<td>Subpart D: Current Good Tissue Practice (CGTP)</td>
<td>Handling and process controls to prevent contamination and introduction, transmission, or spread of communicable diseases</td>
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<td>Subpart E: Additional requirements</td>
<td>Adverse reactions and deviation reporting and labeling</td>
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<td>Subpart F: Inspection and enforcement</td>
<td>Inspection, importation, orders of retention, recall, destruction and cessation of manufacturing</td>
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</tbody>
</table>
Donor Eligibility (DE) Determination
(§ 1271.50)

- A donor eligibility (DE) determination is based on screening and testing of HCT/P donors for relevant communicable disease agents and diseases.

- A DE determination is required for all donors of cells and tissues (HCT/Ps), except as provided in § 1271.90.

- An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible, except as provided in §§ 1271.60(d), 1271.65(b), and 1271.90.
What are Relevant Communicable Disease Agents or Diseases (RCDADs)?

(§ 1271.3(r), 2007 DE Guidance III.D., 2016 Zika Guidance)

For all cells and tissues:
- Human immunodeficiency virus, types 1 and 2 (HIV-1/2)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Human transmissible spongiform encephalopathy (hTSE), including Creutzfeldt-Jakob disease (CJD)
- *Treponema pallidum* (agent that causes syphilis)
- Vaccinia* 
- Sepsis*
- West Nile Virus (WNV)*
- Zika Virus (ZIKV)*

For viable, leukocyte-rich cells and tissues:
- Human T-lymphotropic virus, type I and type II (HTLV-I/II)

For reproductive cells and tissues:
- *Chlamydia trachomatis* (CT)
- *Neisseria gonorrhoea* (NG)

* Identified as RCDADs under § 1271.3(r)(2); notified through Guidance
When is a Donor Eligible?

(§ 1271.50)

- Donor screening (described in § 1271.75) must indicate that the donor:
  - Is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases; and
  - Is free from communicable disease risks associated with xenotransplantation.

- Donor testing results for relevant communicable disease agents (described in § 1271.80 and § 1271.85) must be negative or nonreactive, except as provided in § 1271.80(d)(1).
WHAT ARE THE DONOR SCREENING REQUIREMENTS?
Donor Screening: Ineligible Donors

(§ 1271.75)

- Any communicable disease risk associated with xenotransplantation.
- A risk factor for or clinical evidence of any of the RCDADs for which screening is required.

<table>
<thead>
<tr>
<th>RCDADs</th>
<th>All Donors (1271.75(a))</th>
<th>Donors of viable, leukocyte-rich cells or tissue (1271.75(b))</th>
<th>Donors of reproductive cells or tissue (1271.75(c))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HBV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HCV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>hTSE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>T. pallidum</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WNV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ZIKV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sepsis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HTLV</td>
<td>✓ (semen only)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Neisseria gonorrhoea</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
What are relevant medical records?

- Relevant Medical Records
  - § 1271.3(s)
- Current Donor Medical History Interview
  - § 1271.3(n)
- Current Report of the Physical Assessment/Examination
- Other Records (If Available)
- Additional Lab Test Results
- Medical Records
- Coroner & Autopsy Reports
- Relevant Information from Other Sources

§ 1271.75, 1271.3(s) & DE Guidance IV.C.
Risk Factors or Conditions

- You must review the relevant medical records and ask questions about the donor’s medical history and relevant social behavior, including risk factors for RCDADs, and communicable disease risks associated with xenotransplantation

- DE Guidance, section IV.E.
  - List of conditions and behaviors that increase the donor’s relevant communicable disease risk
Clinical Evidence

• You must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (§ 1271.75).

• For cadaveric donors, you should:
  • Determine whether an autopsy was not performed due to a perceived risk of transmission of a communicable disease, or,
  • If an autopsy was performed, whether any special precautions were taken that would suggest there was special concern over the risk of transmission of a communicable disease from the donor.

• DE Guidance, section IV.F.
  • Examples of clinical evidence of relevant communicable disease
Physical Evidence

• You should review the records of the physical assessment or physical examination for any signs that may indicate high-risk behavior for or infection with a relevant communicable disease.

  • You may rely on records of a recent report of a physical examination by other health professionals.

  • For living donors, you may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records.

• DE Guidance, section IV.G.

  • Examples of physical evidence of relevant communicable disease or high-risk behavior associated with these diseases
ZIKV Guidance

Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products

Guidance for Industry

This guidance is for immediate implementation.

- Published: March 2016
- Implementation: 4 weeks after guidance was issued
Revise Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have Received Human-Derived Clotting Factor Concentrates

Guidance for Industry

This guidance is for immediate implementation.

- Published: November 2016
- Implementation: As soon as relevant procedures have been updated
WHAT ARE THE DONOR TESTING REQUIREMENTS?
General Testing Requirements

(§ 1271.80(c))

Testing must be performed:

- Using appropriate FDA-licensed, approved, or cleared donor screening tests
  - Appropriate tests for chlamydia and gonorrhea are discussed under § 1271.80(c)
- According to the manufacturer’s instructions for use (IFU)
- Use a test specifically labeled for cadaveric specimens instead of a more generally labeled test when applicable and when available
- In a CLIA-certified laboratory (Clinical Laboratory Improvement Amendments of 1988)
  - Or equivalent as determined by the Centers for Medicare and Medicaid Services (CMS)
Timing of Specimen Collection

(§ 1271.80(b))

• General: specimen to be used for donor testing must be collected at the time of recovery, or within 7 days before or after recovery of HCT/Ps

• Oocyte & certain Hematopoietic Stem/Progenitor Cell (HPC) Donors: specimen for testing may be collected up to 30 days prior to or within 7 days after HCT/P recovery

• Note: this 30 day collection time does NOT extend to semen donors
## Testing a donor for RCDADs

Test a donor specimen for evidence of infections due to:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 1/2</td>
<td>All</td>
</tr>
<tr>
<td>HBV</td>
<td>All</td>
</tr>
<tr>
<td>HCV</td>
<td>All</td>
</tr>
<tr>
<td><em>T. Pallidum</em></td>
<td>All</td>
</tr>
<tr>
<td>WNV</td>
<td>Living</td>
</tr>
<tr>
<td>HTLV I/II</td>
<td>Viable, leukocyte-rich</td>
</tr>
<tr>
<td>CMV*</td>
<td>Viable, leukocyte-rich</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Reproductive</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Reproductive</td>
</tr>
</tbody>
</table>

*CMV is not an RCDAD. You must establish and maintain a standard operating procedure governing the release of an HCT/P from a donor whose specimen tests reactive for CMV.*
# Adequate and Appropriate Tests

<table>
<thead>
<tr>
<th>HIV-1</th>
<th>HBV</th>
<th>Chlamydia trachomatis</th>
<th>Neisseria gonorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FDA licensed screening test:</td>
<td>• FDA licensed screening test:</td>
<td>• FDA cleared diagnostic test for detection of:</td>
<td>• FDA cleared diagnostic test for detection of:</td>
</tr>
<tr>
<td>• Anti-HIV-1 or combo test for anti-HIV-1 and anti-HIV-2, AND</td>
<td>• Hepatitis B surface antigen (HBsAg), AND</td>
<td>• NAT test for CT in an asymptomatic, low-prevalence population</td>
<td>• NAT test for NG in an asymptomatic, low-prevalence population</td>
</tr>
<tr>
<td>• NAT test for HIV-1 or combination NAT test</td>
<td>• Total antibody to Hepatitis B core antigen (IgG &amp; IgM; anti-HBc)</td>
<td>• NAT test for HBV</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-2</th>
<th>HCV</th>
<th>CMV</th>
<th>Treponema pallidum</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FDA licensed screening test:</td>
<td>• FDA licensed screening test:</td>
<td>• FDA cleared screening test:</td>
<td>• FDA cleared screening test:</td>
</tr>
<tr>
<td>• Anti-HIV-2 or combo test for anti-HIV-1 and HIV-2</td>
<td>• Anti-HCV, AND</td>
<td>• Anti-CMV, total IgG and IgM</td>
<td>• Nonreponemal or treponemal</td>
</tr>
<tr>
<td></td>
<td>• NAT test for HCV or combination test</td>
<td>• NAT test for WNV</td>
<td></td>
</tr>
</tbody>
</table>

**HTLV-I/II**

<table>
<thead>
<tr>
<th>HTLV-I/II</th>
<th>WNV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FDA licensed screening test:</td>
<td>• FDA licensed screening test:</td>
</tr>
<tr>
<td>• Anti-HTLV-I/II</td>
<td>• NAT test for WNV</td>
</tr>
</tbody>
</table>

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Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products

Guidance for Industry

- Published: August 2016
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)

Guidance for Industry

Published: September 2016
Ineligible Donors

- A donor whose specimen tests reactive on a screening test for a communicable disease agent in accordance with 1271.85
  - Exception – a donor whose specimen tests reactive on a nontreponemal screening test for syphilis and negative on a specific treponemal confirmatory test
- A donor in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected.
  - See also DE Guidance, sections V.F. & V.G.
WHAT ARE THE EXCEPTIONS TO THE DE RULE?
DE Determination Not Complete

(§ 1271.60(d))

Use of an HCT/P from a donor for whom the DE determination is not complete is not prohibited if there is a documented urgent medical need for the HCT/P

- Urgent medical need means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P (§ 1271.3(u))
- Special labeling and physician notification requirements apply (§ 1271.60(d)(2-3))
- You must complete the donor eligibility determination during or after the use of the HCT/P, and you must inform the physician of the results of the determination (§ 1271.60(d)(4))
Ineligible Donors

(§ 1271.65(b))

- Implantation, transplantation, infusion, or transfer of an HCT/P from an ineligible donor is permitted under the following conditions:
  - Allogeneic use in a first-degree or second-degree blood relative
  - Reproductive cells or tissue from a directed reproductive donor (defined under § 1271.3(l))
  - Documented urgent medical need (defined under § 1271.3(u))
  - Special labeling & notification requirements apply (§ 1271.65(b)(2)-(3))
  - Document that you notified physician of results of RCDAD testing and screening

- Nonclinical Use:
  - For special labeling requirements, see § 1271.65(c)
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 (other than embryos) originally exempted (at time of donation) but subsequently intended for direct donation, provided that:
   • additional donations are unavailable (e.g., due to infertility or health condition of the donor), and
   • appropriate measures are taken to screen and test the donor(s) before transfer to the recipient

4. Embryos originally exempted (at time of cryopreservation) but subsequently intended for directed or anonymous donation*
   • appropriate measures should be taken to screen and test the donor(s) before transfer to the recipient when possible

迦 Special labeling requirements (1271.90(c))
Exceptions for reproductive use

(§ 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.

• Does not create an exception for deficiencies that occurred in making the DE determination for either the oocyte donor or the semen donor 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.

➢ Special labeling requirements (1271.90(c))
ADDITIONAL INFORMATION ABOUT ZIKA VIRUS
Testing Donors for ZIKV

- Currently, FDA does not provide any recommendations on donor testing
- FDA is committed to working with U.S. government partners and manufacturers interested in developing tests for HCT/P donors
- FDA will consider appropriate recommendations for use of such tests upon their availability
Testing Donors for ZIKV

- If donor testing is performed:
  - Results must be included in the donor’s relevant medical records
  - A reactive/positive test is considered a risk factor, even if an investigational test was used
  - A nonreactive/negative test does not override any risk factors identified in the March 2016 ZIKV guidance

- Limited uses of HCT/P from ineligible donors:
  - § 1271.65(b)

- Donor eligibility determination not required:
  - § 1271.90(a)

- Exceptions for reproductive use:
  - § 1271.90(b)
ZIKV in Cells and Tissues from Living Donors

- **Semen:**
  - ZIKV RNA Detected 6 months after infection (Barzon, 2016; Nicastri, 2016)
  - Infectious ZIKV isolated from semen 69 days after symptom onset (Arsuaga, 2016)
  - Detected in cellular component of semen (Barzon, 2016)
  - Transmission has occurred from asymptomatic males (Freour, 2016; Brooks, 2016)

- **Gestational tissues:**
  - ZIKV identified in human amnion and umbilical cord; replicates in human placental macrophages, placental fibroblast, and umbilical cord mesenchymal stem cells (El Costa, 2016; Jurado, 2016; Tabata, 2016; van der Eijk, 2016)
  - Infections early and late in pregnancy associated with infected gestational tissues and fetal tissues; third trimester placentas positive for ZIKV RNA when infection occurred during first trimester (Bhatnagar, 2017)
ZIKV Research

Two studies are currently underway to evaluate Zika virus in non-human primates (NHPs):

- **ZIKV Macaque Tissue Testing (University of California, Davis)**
  - FDA Contract
  - The study will conduct testing of samples obtained during initial evaluation of a NHP model of Zika virus disease
  - [http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm537724.htm](http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm537724.htm)

- **Examination of Zika Virus Tissue Tropism Throughout Pregnancy (University of Wisconsin, Madison)**
  - NIAID Grant Supplement
  - Co-funded by HRSA and FDA Office of the Chief Scientist, Office of Counterterrorism and Emerging Threats
  - The study will assess cells and tissues that support growth of Zika virus, and the duration of Zika viral RNA in body tissues during pregnancy in NHP
References

Tissue Homepage
http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm

Code of Federal Regulations Title 21
http://www.ecfr.gov/cgi-bin/text-idx?SID=ae1deec79a9f185d48af015ae277f5d&mc=true&tpl=/ecfrbrowse/Title21/21cfr1271_main_02.tpl

Testing HCT/P donors for RCDADs

Tissue Guidance Documents

Donor Eligibility

Human-Derived Clotting Factor Concentrates

WNV NAT

HBV NAT

Zika Virus
Contact Information

Manufacturers Assistance
Industry.Biologics@fda.hhs.gov

Consumer Questions About Products
ocod@fda.hhs.gov

Regulatory Questions
CBEROCTGTRMS@fda.hhs.gov