21 CFR Part 1271: HCT/P Regulatory Framework- Part 2

FDA Small Business Regulatory Education for Industry (REdI)
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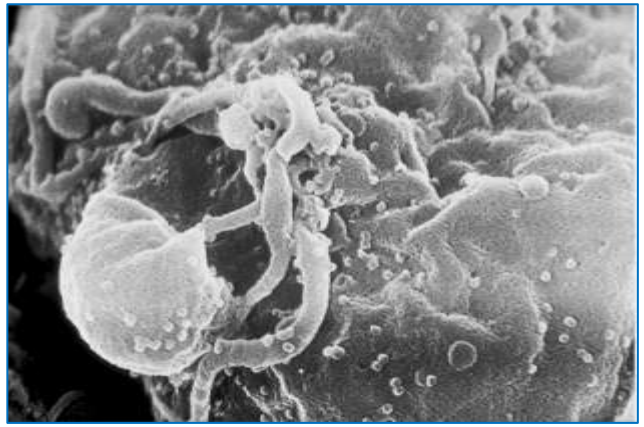
Human Cells, Tissues, or Cellular or Tissue-Based Products (HCT/Ps)- Donor Eligibility



Human Immunodeficiency Virus
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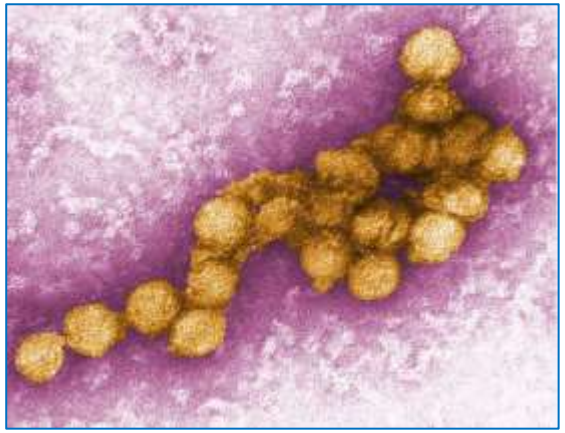

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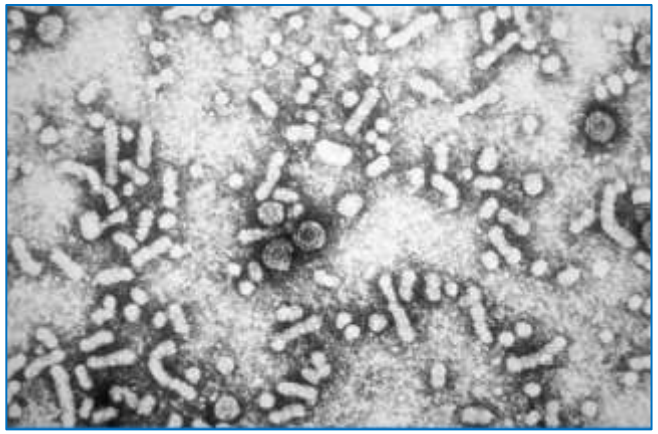

Hepatitis B Virus
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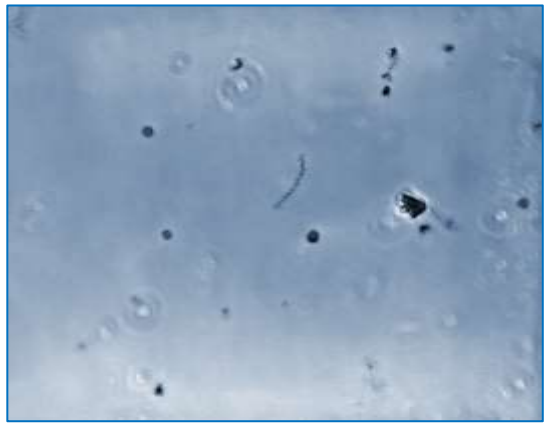

Treponema pallidum
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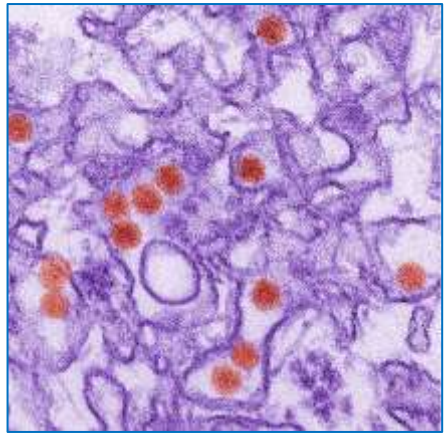


Zika Virus
https://phil.cdc.gov/Details.aspx?pid=20538

Learning Objectives

- Describe the purpose and applicability of HCT/P donor eligibility (DE) rule in 21 CFR part 1271, subpart C
- Describe the requirements for donor screening, donor testing, and making a DE determination
- Identify tips for submitting a request for an exemption or alternative

Note: Presentation does not include a complete list of regulatory requirements. Refer to 21 CFR part 1271 and applicable guidance documents.

HCT/P DE Rule (21 CFR part 1271, subpart C): Purpose and Applicability

21 CFR part 1271 (Effective May 25, 2005)

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

Note: Subparts C and D also apply to HCT/Ps regulated as drugs, devices, and/or biologics

What is the purpose of the DE rule?

- Increase the safety of HCT/Ps and public confidence in their safety
- Prevent the introduction, transmission and spread of communicable diseases.

DE rule applicability

- HCT/Ps recovered on or after May 25, 2005
  - HCT/Ps regulated solely under the authority of section 361 of the Public Health Service (PHS) Act (361 HCT/Ps) and subject to 21 CFR part 1271 (pre-market review not required)
  - HCT/Ps regulated as drugs, devices, and/or biological products under authority of section 351 of the PHS Act and/or the Food, Drug & Cosmetic (FD&C) Act and subject to 21 CFR part 1271 and premarket review requirements (e.g., investigational new drug (IND) application, biological license application (BLA))

§ 1271.1(b)

DE Determination

What is DE determination?

- A DE determination is based on screening and testing of HCT/P donors for ***relevant communicable disease agents and diseases (RCDADs)***.
- A DE determination is required for all donors of HCT/Ps, except as provided under § 1271.90.
- An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible, with some exceptions (§§ 1271.60(d), 1271.65(b), and 1271.90).

What are RCDADs?

Two groups of RCDADs:

- Those specifically listed in the regulations (§1271.3(r)(1))
- Those that meet the definition of RCDAD and notified through guidance documents (§1271.3(r)(2))

What Are RCDADs? (continued)

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) and variant CJD (vCJD)
- *Treponema pallidum* (agent that causes syphilis)
- Vaccinia
- Sepsis
- West Nile Virus (WNV)
- Zika Virus (ZIKV)

Identified as RCDADs under § 1271.3(r)(2); notified through Guidance

For viable, leukocyte-rich cells and tissues, RCDADs also include:

- Human T-lymphotropic virus, type I and type II (HTLV-I/II)

For reproductive cells and tissues, RCDADs also include:

- *Chlamydia trachomatis* (CT)
- *Neisseria gonorrhea* (NG)

§ 1271.3(r), DE Guidance, ZIKV Guidance

When is a donor eligible?

- **Donor screening** 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 must be negative or nonreactive (exception provided for tests for syphilis).

§§ 1271.50, 1271.75, 1271.80, 1271.85

Accompanying records

- Once a DE determination has been made, the following must accompany the HCT/P at all times:
  - A distinct identification code affixed to the HCT/P container
  - A statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible, and
  - A summary of the records used to make the DE determination

§§ 1271.55

When is a DE determination not required?

- Donor screening, donor testing, and making a DE determination not required for:
  - Cells and tissue for autologous use; or
  - Certain reproductive cells and tissues for reproductive use
- Must comply with applicable labeling requirements

§ 1271.90(a)-(c)

Limited use of HCT/Ps from ineligible donors

- An HCT/P from a donor who has been determined ineligible is not prohibited in the following circumstances:
  - HCT/P is for allogeneic use in a first- or second-degree blood relative
  - Reproductive cells and tissues from a directed reproductive donor as defined in § 1271.3(l); or
  - There is documented urgent medical need as defined in § 1271.3(u)
- Must comply with applicable requirements for labeling and notification of the physician using the HCT/P

§ 1271.90(a)-(c)

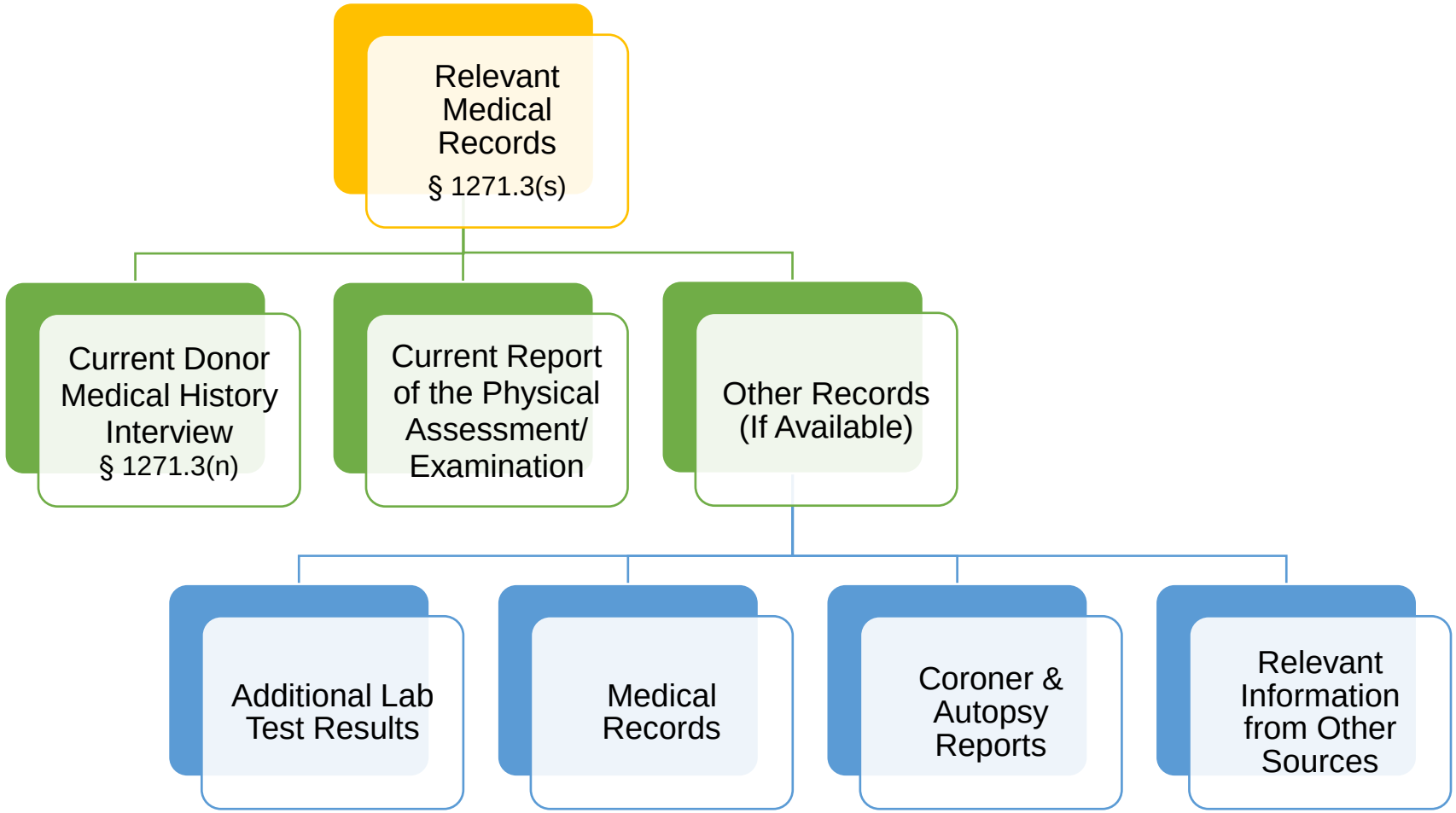
Donor Screening

How do you screen a donor?

- You must review donor's **relevant medical records** for
  - risk factors for, and clinical evidence of, infection due to RCDADs; and
  - communicable disease risks associated with xenotransplantation.
- A donor must be determined ineligible if a risk factor for or clinical evidence of any RCDAD or communicable disease risk associated with xenotransplantation is identified.

§ 1271.75

What are relevant medical records?



§ 1271.3(s), 1271.3(o), 1271.3(n), 1271.75, and DE Guidance IV.C

What are relevant medical records? (cont.)

- Donor medical history interview asks questions about the donor's medical history and relevant social behavior, including risk factors for RCDADs, and communicable disease risks associated with Xenotransplantation
- Review relevant medical records for clinical evidence of RCDADs
- Review the records of the physical assessment or physical examination for any sign that may indicate high-risk behavior for or infection with a RCDAD

§ 1271.75, DE Guidance IV.C and E-G, ZIKV Guidance

Donor screening for RCDADs

RCDADs	All Donors (1271.75(a))	Donors of viable, leukocyte-rich cells or tissue (1271.75(b))	Donors of reproductive cells or tissue (1271.75(c))
HIV	✓	✓	✓
HBV	✓	✓	✓
HCV	✓	✓	✓
hTSE	✓	✓	✓
T. pallidum	✓	✓	✓
WNV	✓	✓	✓
ZIKV	✓	✓	✓
Sepsis	✓	✓	✓
Vaccinia	✓	✓	✓
HTLV		✓	✓ (semen only)
Chlamydia trachomatis			✓
Neisseria gonorrhea			✓

§ 1271.75, DE Guidance III.C –D and ZIKV Guidance

Donor Testing

What are general donor testing requirements?

Timing of specimen collection:

- Specimens for donor testing must be collected at the time of recovery cells or tissue, or ***within 7 days*** before or after recovery, except for
  - Donors of peripheral blood stem/progenitor cells, bone marrow (if not excepted under 1271.3(d)(4)), or oocytes, specimen for testing may be collected up to ***30 days before*** recovery.

§ 1271.80(b)

What are general donor testing requirements? (cont.)

Testing must be performed:

- Using appropriate FDA-licensed, approved, or cleared donor screening tests
- According to the manufacturer's instructions for use
- By a laboratory that is CLIA (Clinical Laboratory Improvement Amendments of 1988) certified or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services

§ 1271.80(c)

Donor testing for RCDADs

Pathogen	Donors
HIV 1/2	All
HBV	All
HCV	All
T. pallidum	All
WNV	Living**
HTLV I/II	Viable, leukocyte-rich
CMV*	Viable, leukocyte-rich
Chlamydia trachomatis	Reproductive***
Neisseria gonorrhea	Reproductive***

* CMV is not an RCDAD. Must have a procedure for release of an HCT/P from a donor whose specimen tests reactive for CMV.

** WNV testing: June 1st – October 31st in U.S. (50 states + D.C.; year-round elsewhere)

*** Unless recovered using a method that ensures freedom from contamination infectious disease organisms that may be present in the GU tract

§ 1271.85

Adequate and Appropriate Tests

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

HIV-2
• FDA licensed screening test:
  • Anti-HIV-2 or combo test for anti-HIV-1 and HIV-2
	HCV
	• FDA licensed screening test:
	  • Anti-HCV, **AND**
	  • NAT test for HCV or combination test
		CMV
		• FDA cleared screening test:
		  • Anti-CMV, total IgG and IgM
			Treponema pallidum
			• FDA cleared screening test:
			  • Nontreponemal or treponemal

HTLV-I/II
• FDA licensed screening test:
  • Anti-HTLV-I/II
	WNV
	• FDA licensed screening test:
	  • NAT test for WNV
		DE Guidance, sections VI.A.-B.
		Syphilis Guidance
		WNV Guidance
		HBV NAT Guidance	

FDA-licensed, approved, or cleared tests

- "Testing HCT/P Donors for Relevant Communicable Disease Agents and Diseases"

  https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable

- "Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays"

  https://www.fda.gov/vaccines-blood-biologics/complete-list-donor-screening-assays-infectious-agents-and-hiv-diagnostic-assays

Request for an Exemption or Alternative (21 CFR 1271.155)

What if requirements are not met?

- May request an exemption from or alternative to any requirement in part 1271 subpart C (Donor Eligibility) or subpart D (Current Good Tissue Practice)
- Requests must be submitted to the OTAT Office Director
- Must include:
  - Information justifying the requested exemption from the requirement, or
  - A description of a proposed alternative method of meeting the requirement
- Must not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted

§ 1271.155

What if requirements are not met? (cont.)

- FDA would consider granting an exemption or alternative requested under § 1271.155, if such action is consistent with the goals of protecting the public health and the information submitted justifies an exemption or alternative.
- Refer to Exemptions and Alternatives webpage at https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/exemptions-and-alternatives

Helpful tips for submitting a request for an exemption or alternative

For HCT/Ps regulated as drugs, devices and/or biological products, we encourage sponsors to:

- Discuss the request during early communications with the FDA (e.g., INTERACT, Pre-IND meeting)
- Submit the request prior to submitting the IND/IDE application to ensure adequate time for FDA to review

Note: An IND/IDE may be placed on hold if regulations are not met and a request for an exemption or an alternative method has not yet been granted.

Helpful tips for submitting a request for an exemption or alternative (cont.)

- Include supporting documentation and relevant valid scientific data regarding how risk of communicable disease transmission is mitigated
  - Description of the manufacturing process of your product
  - Description of donor eligibility determination, donor screening and donor testing
  - In-process and final product testing performed during your manufacturing process to mitigate the risk of communicable disease transmission

Knowledge Check

Knowledge check 1

Donor eligibility requirements are applicable to:

1. HCT/Ps regulated solely under the authority of section 361 of the Public Health Service (PHS) Act (361 HCT/Ps)
2. HCT/Ps regulated as drugs, devices, and/or biological products under authority of section 351 of the PHS Act and/or the Food, Drug & Cosmetic (FD&C) Act
3. 1 and 2

Knowledge check 2

An HCT/P donor eligibility determination is based on the results of:

1. Donor screening only
2. Donor testing only
3. Donor screening and donor testing

Resources:

- 21 CFR part 1271
- Tissue Guidances webpage:
  - Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007)
  - Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue-Based Products for Infection with Treponema pallidum (Syphilis) (September 2015)
  - 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 (August 2016)
  - Revised Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have Received Human-Derived Clotting Factor Concentrates (November 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) (September 2016, Corrected May 2017)
  - Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products (March 2016, Updated May 2018)
  - Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (December 2011)

Summary

- Donor eligibility requirements are applicable to all HCT/Ps regardless of how they are regulated.
- Donor screening and testing for RCDADs are required for making a DE determination.
- You may consider submitting a request for an exemption or alternative with the FDA if the DE or CGTP requirements are not met.

Contact information

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- **OTAT Learn Webinar Series:**

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