U.S. FOOD & DRUG ADMINISTRATION

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Donor Screening

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Overview

Describe all donor screening criteria as recommended in final guidance for HCT/Ps, including

- conditions and behaviors,
- clinical evidence, and
- physical evidence

that increase a donor's relevant communicable disease risk.

Abbreviations

- **DE** – Donor Eligibility
- **RCDAD** – Relevant Communicable Disease Agent or Disease
- **HIV** – Human Immunodeficiency Virus
- **HBV** – Hepatitis B Virus
- **HCV** – Hepatitis C Virus
- **HTLV** – Human T-lymphotropic virus
- **WNV** – West Nile virus
- **ZIKV** – Zika virus
- **CMV** – Cytomegalovirus
- **§** - Section (of the rule) ex. §1271.3
- **HPC** – Hematopoietic stem / progenitor cells
- **STI** – Sexually transmitted infection
- **ID** – Individual Donor
- **BV** – Blood Volume
- **PV** – Plasma Volume
- **TSE** – transmissible spongiform encephalopathy
- **CJD** – Creutzfeldt-Jakob disease
- **vCJD** – variant Creutzfeldt-Jakob disease
- **NAT** – Nucleic Acid Amplification Technology or "Nucleic Acid Test" (includes Polymerase Chain Reaction (PCR) and Transcription-Mediated Amplification (TMA))
- **UDRAI** – Uniform Donor Risk Assessment Interview
- **C/W** – consistent with

Regulatory Basis for Donor Screening

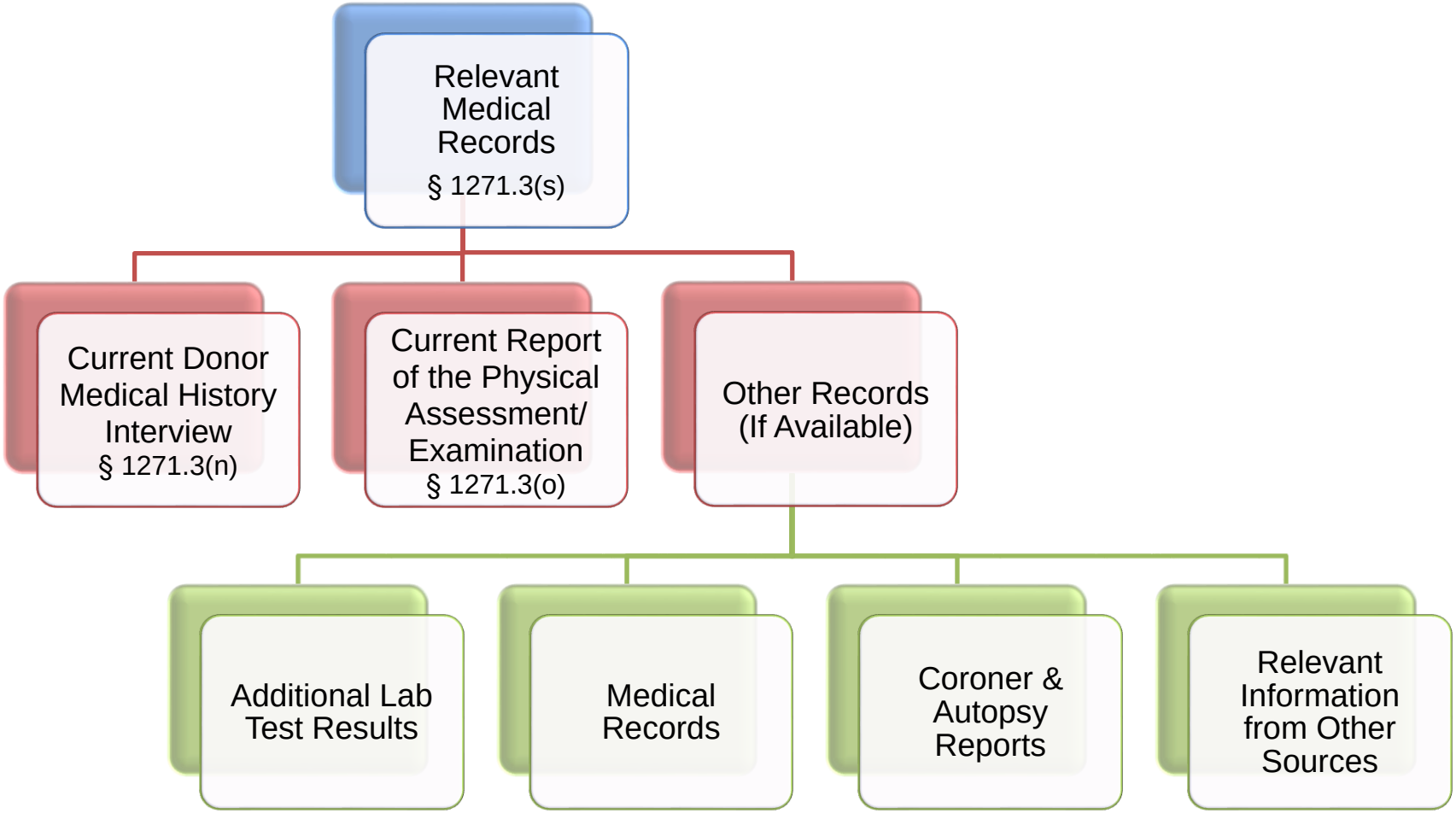
§ 1271.75(a)

All donors:

- Except as provided under § 1271.90, if you are the establishment that performs donor screening, you must screen a donor of cells or tissue by reviewing the donor's ***relevant medical records*** for:
  - Risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, and risks associated with xenotransplantation
  - Additional requirements for viable, leukocyte-rich HCT/Ps
  - Additional requirements for reproductive HCT/Ps

Relevant Medical Records

§ 1271.75 & DE Guidance IV.C.



Relevant Communicable Disease Agents and Diseases (RCDADs)

§ 1271.75(a)

Agent	Applies to	Screening	Testing*
HIV-1 and -2	All	X	X
Hepatitis B Virus	All	X	X
Hepatitis C Virus	All	X	X
Syphilis	All	X	X
TSE	All	X	
WNV	All	X	LIVING DONORS
ZIKV	All	X	
Sepsis	All	X	
Vaccinia (recent smallpox vaccination)	All	X	
HTLV-I and II	Viable, leukocyte-rich HCT/Ps	X	X
CMV**	Viable, leukocyte-rich HCT/Ps		X
Chlamydia trachomatis	Reproductive HCT/Ps	X	X
Neisseria gonorrhoeae	Reproductive HCT/Ps	X	X

* More than one test may be necessary to adequately and appropriately test for a single RCDAD (e.g. serology and NAT).

** CMV is not an RCDAD. Donors of viable leukocyte-rich HCT/Ps must be tested for CMV, and positive test results must be communicated to the responsible physician.

CONDITIONS AND BEHAVIORS

Conditions and Behaviors

DE Guidance, IV.E.

The following slides list conditions and behaviors that increase the donor's relevant communicable disease risk. Except as noted in this section, and in accordance with § 1271.75(d), you should determine to be *ineligible* any potential donor who exhibits one or more of the following conditions or behaviors:

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

1. Men who have had sex with another man (MSM) in the preceding 5 years (risk factor for HIV, HBV).
2. Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, or subcutaneous injections (risk factor for HIV, HBV HCV)

http://www.thehillscenter.com/images/article_images/addiction_iv-drug-use.gif

Conditions and Behaviors

DE Guidance, IV.E.

3. Persons with hemophilia or other related clotting disorders who have received human-derived clotting factor concentrates* in the preceding [illegible] years (risk factor for HIV, HBV, [illegible]).
   - A donor who received clotting factors once to treat an acute bleeding event more than 12 months ago may be eligible to donate.

http://www.24remedy.com/wp-content/uploads/2014/11/Hemophilia.jpg

*Human derived clotting factor concentrates are considered "high-risk" because they are derived from pooled human plasma.

Guidance: *"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"*

Clotting Factors Guidance (2016)

- HDCFCs no longer considered to be a risk factor for HIV, HBV, or HCV
- HCT/P donors should not be considered ineligible due to the following conditions, and screening for these conditions is no longer necessary:
  1. Persons with hemophilia or other related clotting disorders who have received HDCFCs at any time;
  2. Persons who received clotting factors once to treat an acute bleeding event at any time; or
  3. Persons who have had sex at any time with either of the persons described above
- Supersedes the recommendations listed in section IV.E.3. of the 2007 DE Guidance
- Published: November 1, 2016
- Implementation: As soon as relevant procedures have been updated

Risk Factors and Conditions

DE Guidance, IV.E.

4. Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years (risk factor for HIV, HBV, HCV).
5. Persons who have had sex in the preceding 12 months with any person described in criteria 1 through 4 of this section or with any person who has HIV infection, including a positive or reactive test for HIV, hepatitis B infection, or clinically active (symptomatic) hepatitis C infection.
6. Persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV, and/or HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane.

What was wrong with the previous slide?

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

7. Children born to mothers with or at risk for HIV infection:
   - if 18 months of age or younger, or
   - if breast-fed within the preceding 12 months.

   Note: We do not recommend deferral of a donor who is a child born to a mother with or at risk for HIV infection if the child is over 18 months of age and has not been breast-fed within the preceding 12 months, provided that the child's HIV antibody tests, physical examination, and medical records do not indicate evidence of HIV infection.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

8. Persons who have been in juvenile detention, lock up, jail or prison for more than <u>72 consecutive hours in the preceding 12 months</u> (risk factor for HIV, HBV, HCV).

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Conditions and Behaviors (Continued)

DE Guidance, IV.E.

9. Persons who have lived with (resided in the same dwelling) another person who has hepatitis B or clinically active (symptomatic) hepatitis C infection in the preceding 12 months.
10. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

11. Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after their 11th birthday.
    - Unless evidence from the time of illness documents that the hepatitis was identified as being caused by hepatitis A virus, Epstein-Barr Virus (EBV), or cytomegalovirus (CMV).
12. Persons who are deceased and have a documented medical diagnosis of sepsis or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death.
    - For example, if a statement such as “rule-out sepsis” is noted in the medical records, and subsequent notations indicate a diagnosis other than sepsis, a potential donor might still be eligible.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

13. Persons who have had (a) smallpox vaccination (vaccinia virus) in the preceding 8 weeks should be evaluated as follows:
    a. For persons who had no vaccinia complications:
        - You should defer the donor until after the vaccination scab has separated spontaneously, or for 21 days post-vaccination, whichever is the later date, and until the physical examination or physical assessment includes a confirmation that there is no scab at the vaccination site.
        - In cases where a scab was removed before separating spontaneously, you should defer the donor for two months after vaccination.

    Note: We do not recommend deferral of a cadaveric donor who was vaccinated at least 21 days ago and who has no visible scab, if you are unable to obtain a history of how the scab separated.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

b. For persons who have experienced vaccinia complications*, you should defer the donor until 14 days after all vaccinia complications have completely resolved.

   Note: We do not recommend deferral of a cadaveric donor who previously had vaccinia complications but who currently has no visible signs of vaccinia complications, if you are unable to obtain a history of the exact date of resolution of the vaccinia complications.

*Complications of smallpox vaccine or of inadvertent vaccinia virus infection are described as the following:

Eczema vaccinatum
Generalized vaccinia
Progressive vaccinia
Postvaccinial encephalitis
Vaccinial keratitis

See DE Guidance, Appendix 4 for additional information on vaccinia complications.

Conditions and Behaviors (Continued)

DE Guidance, IV.E

14. Persons who acquired a clinically recognizable vaccinia virus infection by contact with someone who received the smallpox vaccine (i.e., touching the vaccination area or the scab, including the covering bandages, or touching clothing, towels, or bedding that might have come into contact with an unbandaged vaccination area or scab).

CDC | CDC Home | Search | Health Topics A-Z

MMWR Weekly

May 4, 2007 / 56(17);417-419

Vulvar Vaccinia Infection After Sexual Contact with a Military Smallpox Vaccinee --- Alaska, 2006

On October 10, 2006, an otherwise healthy woman visited a public health clinic in Alaska after vaginal tears that she had first experienced 10 days before became increasingly painful. The patient reported having a new male sex partner during September 22--October 1, 2006. A viral swab specimen from a labial lesion of the woman was submitted to the Alaska State Virology Laboratory (ASVL) for viral culture. The viral isolate could not be identified initially and subsequently was sent to CDC on January 9, 2007, where the isolate was identified as a vaccine-strain vaccinia virus. After vaccinia was identified, investigators interviewed the woman more closely and learned that her new sex partner was a male U.S. military service member stationed at a local military base. Further investigation determined that the service member had been vaccinated for smallpox 3 days before beginning his relationship with the woman. This report describes the clinical evaluation of the woman and laboratory testing performed to identify the isolate. Health-care providers should be aware of the possibility of vaccinia infection in persons with clinically compatible genital lesions who have had recent contact with smallpox vaccinees.

CDC | CDC Home | Search | Health Topics A-Z

MMWR Weekly

May 22, 2009 / 58(19);532-536

Progressive Vaccinia in a Military Smallpox Vaccinee --- United States, 2009

On May 19, this report was posted as an MMWR Early Release *on the* MMWR *website* (http://www.cdc.gov/mmwr).

Progressive vaccinia (PV), previously known as vaccinia necrosum, vaccinia gangrenosum, or disseminated vaccinia, is a rare, often fatal adverse event after vaccination with smallpox vaccine, which is made from live vaccinia virus (*1*). During recent vaccination programs potential cases of PV were investigated, but none met standard case definitions (*2*). PV has not been confirmed to have occurred in the United States since 1987 (*3*). On March 2, 2009, a U.S. Navy Hospital contacted the Poxvirus Program at CDC to report a possible case of PV in a male military smallpox vaccinee. The service member had been newly diagnosed with acute mylegenous leukemia M0 (AML M0). During

Conditions and Behaviors (Continued)

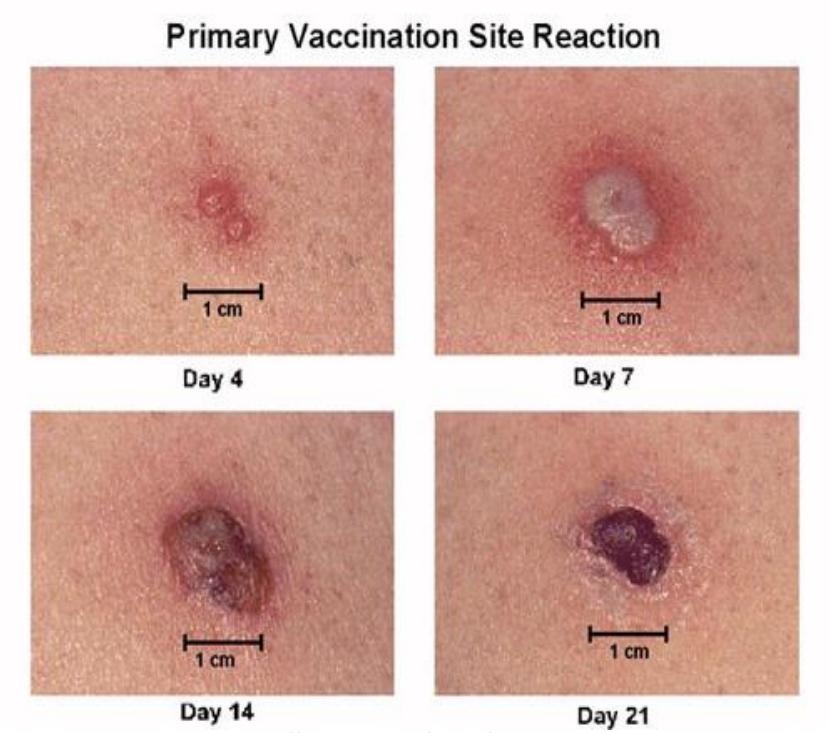
DE Guidance, IV.E.

- For living donors who developed skin lesions as a result of contact with someone who received the smallpox vaccine, you should question the donor regarding the loss of the scab, and you should examine the skin. For cadaveric donors, you should examine the skin.

- If no scab is present, we do not recommend deferral of:
  - a cadaveric donor;
  - a living donor if the scab spontaneously separated; or
  - after three months from the date of vaccination of the vaccine recipient, a living donor whose scab was otherwise removed.

- If a scab is present, you should consider:
  - a cadaveric donor to be ineligible; or
  - a living donor to be deferred until the scab spontaneously separates.

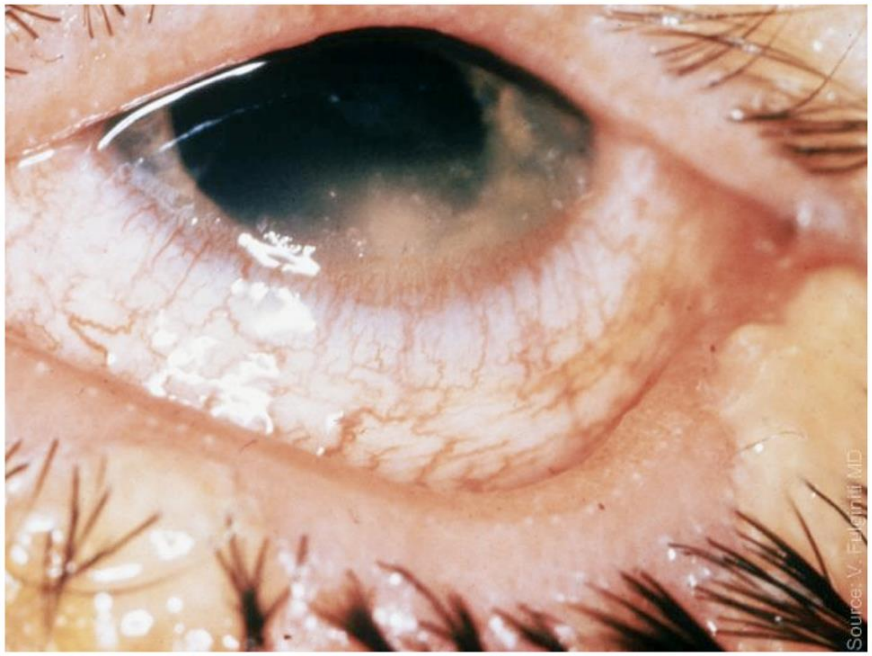
Vaccinia Risk Photos



http://www.bt.cdc.gov/images/VAXSIT5A.jpg

Vaccinia Risk Photos (Continued)

http://www.cdc.gov/mmwr/preview/mmwrhtml/figures/m843a2f2.gif



Cloudy corneal lesions in mother who bathed infant with vaccination and then rubbed her itchy eye. Source: V. Fulginiti MD, digital enhancement © Logical Images.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

- You should defer persons who developed other complications of vaccinia infection acquired through contact with a vaccine recipient until 14 days after all vaccinia complications have completely resolved.

- Note: We do not recommend deferral of a cadaveric donor who previously had complications of vaccinia acquired through contact with a vaccine recipient, but has no visible signs of vaccine complications, if the date of resolution of the vaccinia complications is unknown.

- We do not recommend deferral of contacts who never developed skin lesions or other complications of vaccinia infection.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

15. Persons who have had a medical diagnosis or suspicion of WNV infection (based on symptoms and/or laboratory results, or confirmed WNV viremia) you should defer for 120 days following diagnosis or onset of illness, whichever is later.

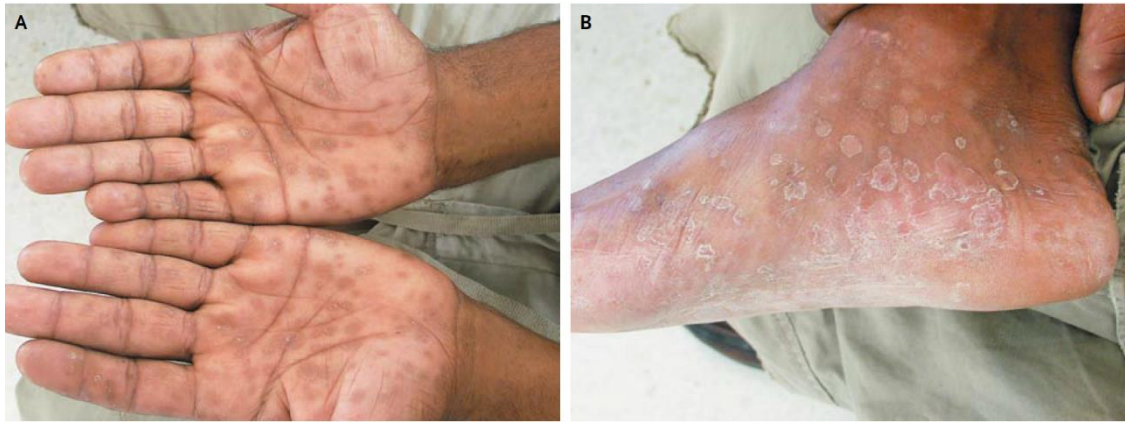
16. Persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days.

CDC PHIL ID#14866

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

17. Persons who have been treated for or had syphilis within the preceding 12 months.
    - We do not recommend deferral of donors if evidence is presented that the treatment occurred more than 12 months ago and was successful.



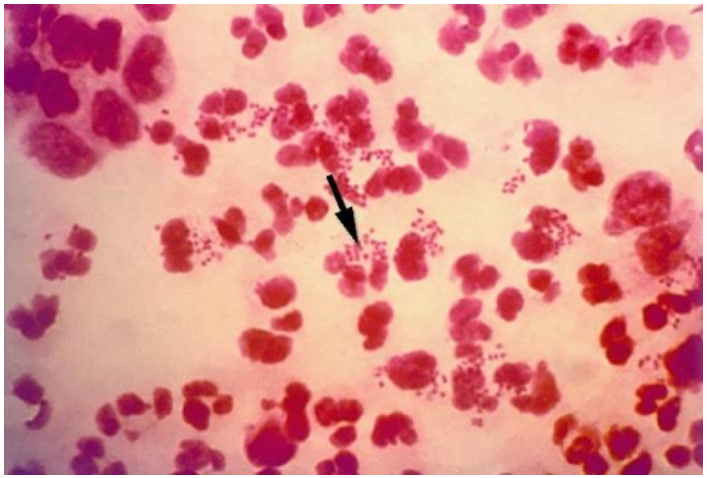
Rash associated with secondary syphilis, Talel Badri, M.D. and Salima Ben Jennet, M.D., Images in Clinical Medicine, N Engl J Med 2011; 364:71

Conditions and Behaviors (Continued)

DE Guidance, IV.E

18. Reproductive HCT/P donors who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection in the preceding 12 months.
    - We do not recommend deferral of persons who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection if evidence is presented that the treatment occurred more than 12 months ago and was successful.

http://www.medicinenet.com/image-collection/chlamydia_picture/picture.htm



http://textbookofbacteriology.net/N.gonorrhoeae1.jpeg

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

Example: A potential donor has a medical record indicating that she was treated for Chlamydia 14 months ago. No follow-up testing was performed at the time of treatment. The medical record serves as evidence that she received treatment more than 12 months ago.

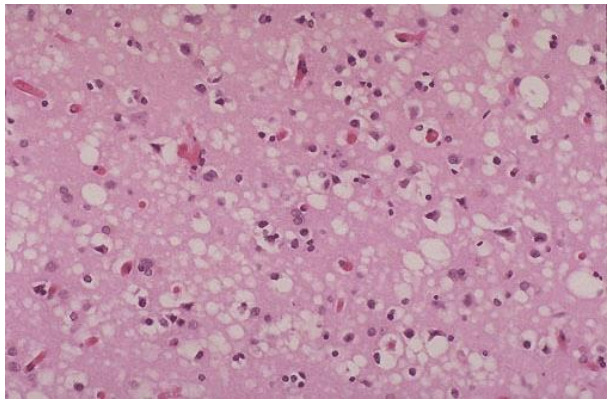
Since the medical record does not include information that a follow-up test was performed after treatment and was negative, there is no evidence that the treatment was successful. However, a current negative test for Chlamydia (as part of the current donor testing) may serve as evidence that the treatment that occurred more than 12 months ago was successful.

Conditions and Behaviors (Continued)

DE Guidance, IV.E

Numbers 19 to 26 in this section are designed to screen for TSEs, including CJD and vCJD.

19. Persons who have been diagnosed with vCJD or any other form of CJD.



http://www.cdc.gov/ncidod/dvrd/cjd/images/classic_cjd_tissue_slide.gif

CJD/vCJD screening questions – If person interviewed is not familiar with the term "Creutzfeldt-Jakob Disease" or "variant CJD" you may try to describe in layman's terms. If the person being interviewed is still not familiar with those terms, <u>you may consider the lack of familiarity with those terms as a negative response to questions using those terms</u>.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

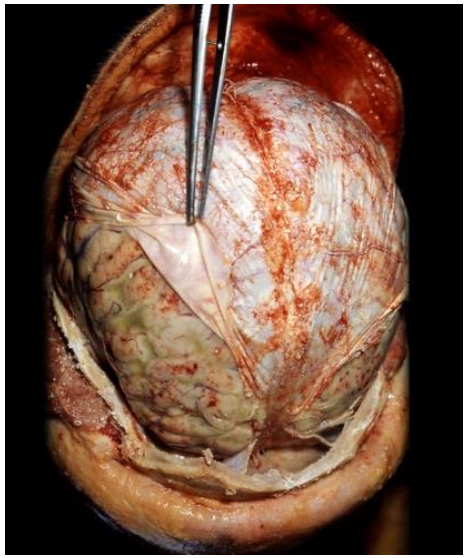
20. Persons who have been diagnosed with:
    - dementia or any degenerative or demyelinating disease of the central nervous system, or
    - other neurological disease of unknown etiology.

Potential donors who have a diagnosis of delirium (e.g., delirium caused by toxic/metabolic diseases or recent head trauma) would not necessarily be considered to have a diagnosis of dementia and should be evaluated by the Medical Director.

HCT/Ps from donors with dementia confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident or brain tumor and who are confirmed not to have evidence of TSE on microscopic examination of the brain may be acceptable based on an evaluation by the Medical Director.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.



http://images.radiopaedia.org/images/25228/1db065474f683a4e0fcbbfeb3fa10a.jpg

21. Persons who are at increased risk for CJD; donors are considered to have an increased risk for CJD <u>if they have received</u>:
    - a non-synthetic dura mater transplant,
    - human pituitary-derived growth hormone, or
    - have one or more blood relatives diagnosed with CJD.

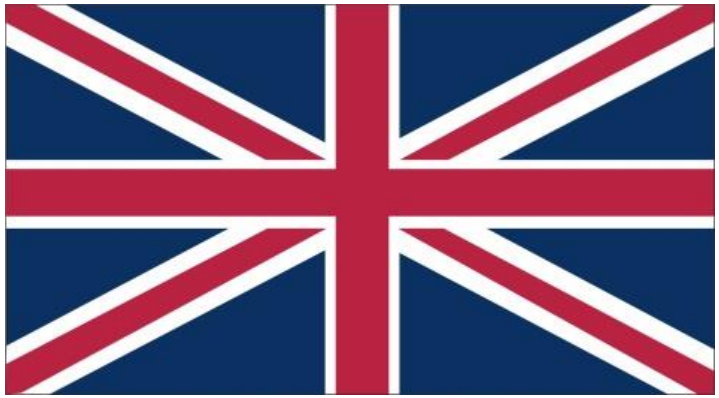
22. Persons who have a history of CJD in a blood relative <u>unless</u>:
    - the diagnosis of CJD was subsequently found to be an <u>incorrect diagnosis</u>;
    - the CJD was <u>iatrogenic</u> (caused by a physician, medical treatment, or therapy); or
    - laboratory <u>testing</u> (gene sequencing) shows that the donor <u>does not have a mutation</u> associated with <u>familial</u> CJD.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

23. Persons who spent three months or more cumulatively in the United Kingdom (U.K.)* from the beginning of 1980 through the end of 1996.

*United Kingdom should include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands. (DE Guidance Appendix 5)



http://www.icicp.org/wp-content/uploads/2014/02/uk-flag.jpg

Conditions and Behaviors (Continued)

DE Guidance, IV.E

24. Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

25. Persons who spent 5 years or more cumulatively in Europe* from 1980 until the present.
    - Note: This criterion includes time spent in the U.K. from 1980 through 1996.
26. Persons who received any transfusion of blood or blood components in the U.K. or France between 1980 and the present.

*Europe includes all of the following: Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom, and Yugoslavia. (DE Guidance Appendix 5)

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

27. Persons or their sexual partners who were born or lived in certain countries in Africa (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria) after 1977 (risk factor for HIV group O).

28. Persons who have received a blood transfusion or any medical treatment that involved blood in the countries listed in criterion 27, after 1977 (risk factor for HIV group O).

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

Note: Establishments utilizing an HIV-1/2 antibody donor screening test that has been licensed by FDA and is specifically labeled in the Intended Use Section of the package insert as sensitive for detection of HIV group O antibodies may delete items 27 and 28 from their screening procedures.

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm180817.htm

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

29. Persons who are xenotransplantation product recipients or intimate contacts of a xenotransplantation product recipient.
    - For this purpose, we define the following terms:
      - Xenotransplantation – procedure that involves the transplantation, implantation, or infusion into a human recipient of either
        - live cells, tissues, or organs from a nonhuman animal source; or
        - human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.
      - Xenotransplantation products include live cells, tissues, or organs used in xenotransplantation.
        - Biological products, drugs, or medical devices sourced from nonliving cells, tissues or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves, are not considered xenotransplantation products.

Conditions and Behaviors (Continued)

DE Guidance, IV.E.

- Xenotransplantation product recipient means a person who undergoes xenotransplantation.
- Intimate contact of a xenotransplantation product recipient means a person who has engaged in activities that could result in intimate exchange of body fluids, including blood or saliva, with a xenotransplantation product recipient.
  - Examples of intimate contacts include sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures.
  - We do not consider sharing of housing or casual contact, such as hugging or kissing without the exchange of saliva, to be intimate contact.

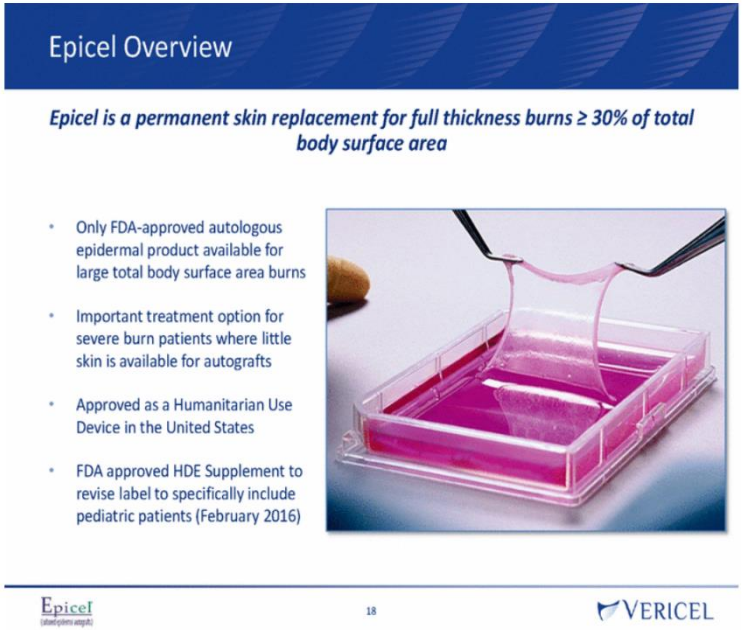
Conditions and Behaviors (Continued)

DE Guidance, IV.E.

Note: There are circumstances in which it might not be necessary to defer a potential HCT/P donor who is an intimate contact of a recipient of certain xenotransplantation products.

For example, an advisory committee recommended and we concur that intimate contacts of persons who have received the product Epicel™ do not need to be deferred from blood donation, because the risk of zoonotic transmission from this product is minimal as the non-human animal cells used in the manufacture of this product originate from a well-characterized cell line.

Epicel®
(cultured epidermal autografts)



Zika Virus (ZIKV)

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

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Guidance for Industry

This guidance is for immediate implementation.

- Publication dates: March 2016, Updated May 2018
- The update supports the continuation of recommendations to screen living donors of HCT/Ps for risks of infection with ZIKV based on geographic areas with risk.

Conditions and Behaviors: ZIKV

Zika Guidance, May 2018

Living donors of HCT/Ps should be considered ineligible if they have any of the following risk factors:

1. Medical diagnosis of ZIKV infection 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 is known to have either of the risk factors listed in items 1 or 2, above.

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf

Conditions and Behaviors: ZIKV (Continued)

Zika Guidance, May 2018

Additionally, donors of umbilical cord blood, placenta, or other gestational tissues should be considered ineligible if the birth mother who seeks to donate gestational tissues has any of the following risk factors:

4. Medical diagnosis of ZIKV infection at <u>any point during that pregnancy</u>.
5. Residence in, or travel to, an area with an increased risk for ZIKV transmission at <u>any point during that pregnancy</u>.
6. Sex at <u>any point during that pregnancy</u> with a person who is known to have either of the risk factors listed in items <u>1 or 2</u>, above.

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf

Conditions and Behaviors: ZIKV (Continued)

Zika Guidance, May 2018

The following non-heart-beating (cadaveric) donors should be considered ineligible:

- Persons with a medical diagnosis of ZIKV infection in the past 6 months.

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Screening Living Donors: ZIKV

Regarding references to use when screening living donors of HCT/Ps:

- First access the CDC webpage for Blood and Tissue Safety.
- To evaluate domestic travel, the "Areas at increased risk for Zika virus transmission through blood or tissue donation in U.S. states" is listed first and continues to be defined at the county level within a state. For the purpose of screening HCT/P donors, do not use other CDC webpages or maps for evaluating travel within the United States.
- For evaluating travel to areas outside of the U.S. states, use the link to the world map and consider countries and territories categorized as "Red" or "Purple" as areas with increased risk of ZIKV transmission. When an area outside the U.S. states becomes shaded as Red or Purple for the first time on the world map, that area and the date of the change will be posted on the Blood and Tissue Safety webpage.
- The CDC webpage for Blood and Tissue Safety should be monitored frequently for any updates.

Testing Donors for ZIKV?

- FDA does not provide any recommendations on donor testing
- If an establishment chooses to test donors for ZIKV:
  - Donors must continue to be screened for ZIKV risks
  - A negative/nonreactive test DOES NOT override recommendations in the 2016 or 2018 ZIKV Guidance
  - A donor with a positive/reactive test is considered ineligible even if no screening risks were identified
  - This applies for any test: licensed, EUA, IND, LDT, etc.
    - Even if a licensed ZIKV donor screening test's intended use includes living, heart-beating, and/or cadaveric donors, that does not mean that a negative test result can be used in place of geographic screening

Why Don't We Have Testing Recommendations?

- ZIKV persists in certain cells and tissues longer than in blood, so a nonreactive/negative NAT blood test does not assure that recovered cells and tissues are not infected with ZIKV
- Correlation of serologic response to ZIKV persistence in cells/tissues is unclear; serology may be unreliable in persons with certain previous infections (e.g., dengue)
- Persistence occurs in symptomatic and asymptomatic individuals
- Examples:
  - ZIKV RNA detected in semen at least 6 months after infection
  - Infectious ZIKV isolated from semen 69 days after symptom onset
  - Sexual transmission has occurred from asymptomatic males
  - ZIKV identified in human amnion and umbilical cord; replicates in human placental macrophages, placental fibroblast, and umbilical cord mesenchymal stem cells
  - 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

Q&A #1

Q1: A living donor has a history of being turned down for blood donation in the past, but she isn't sure of the reason for the deferral. Would she be automatically ineligible to be an HCT/P donor?

Q&A #1

A1: No. Though it would be best to try to determine why the blood donor deferral was made, the tissue regulations and guidance are silent about whether or not a previous blood donation deferral should mean the donor is ineligible to donate HCT/Ps. Sometimes blood establishments have additional or more strict deferral criteria than those that are recommended by FDA for blood donors. The establishment should perform a full donor eligibility determination and if all eligibility criteria are met, the donor may be eligible.

Q&A #1B

Q1b: What if the HCT/P donor had received an HCT/P, such as allograft bone? Does this make the donor ineligible?

A1b: Not necessarily. FDA has not recommended that donors who have had previous HCT/Ps (other than xenotransplants) be ineligible for donation. However, an individual facility may choose not to accept such donors.

Q&A #2

Q2: A reproductive establishment has a potential donor who has a notation in her record that she was treated for chlamydia two years ago. She was given appropriate antibiotic therapy and did not follow up with the health care provider. Could this potential donor be eligible to donate reproductive HCT/Ps?

Q&A #2

A2: Yes, the donor is potentially eligible. The guidance states that "…persons who have been treated for chlamydia or gonorrhea infection may be eligible if evidence is presented that the treatment occurred more than 12 months ago and was successful."

- In this case, the treatment was more than 12 months ago.
- A current chlamydia test (required donor testing) may serve as evidence of successful treatment, if negative.

CLINICAL EVIDENCE

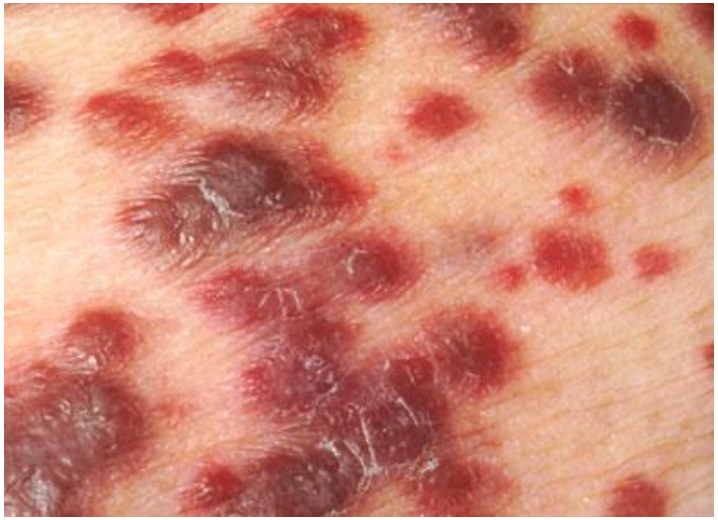
Clinical Evidence

DE Guidance, IV.F.

- You must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases. (§ 1271.75(a))
- You should look for the following examples of clinical evidence of relevant communicable disease.
- Except as noted in this section and in accordance with 1271.75(d), you should determine to be ineligible any potential donor who exhibits <u>one or more</u> of the following examples of clinical evidence of RCDADs:

HIV Clinical Evidence

DE Guidance, IV.F.1.



http://www.avert.org/sites/default/files/image/5474/5474-kaposis-sarcoma-615x300.jpeg

- A prior positive or reactive screening test for HIV;
- Unexplained weight loss;
- Unexplained night sweats;
- Blue or purple spots on or under the skin or mucous membranes typical of Kaposi's sarcoma;
- Disseminated lymphadenopathy (swollen lymph nodes) for longer than one month;

HIV Clinical Evidence (Continued)

DE Guidance, IV.F.1.

- Unexplained temperature of > 100.5°F (38.6°C) for more than 10 days;
- Unexplained persistent cough or shortness of breath;
- Opportunistic infections;
- Unexplained persistent diarrhea; and/or
- Unexplained persistent white spots or unusual blemishes in the mouth.

http://www.etopical.com/wp-content/uploads/2014/04/Viral-Infections-such-as-HIV-and-candida-cause-white-sores.jpg

Viral Hepatitis Clinical Evidence

DE Guidance, IV.F.2.

- A prior positive or reactive screening test for hepatitis B virus or hepatitis C virus;
- Unexplained jaundice;
- *Unexplained* hepatomegaly; and/or
- Past diagnosis of clinical, symptomatic viral hepatitis after the 11th birthday, unless evidence from the time of illness documents that the hepatitis was identified as caused by hepatitis A virus, EBV, or CMV.

Viral Hepatitis Clinical Evidence (Continued)

DE Guidance, IV.F.2.

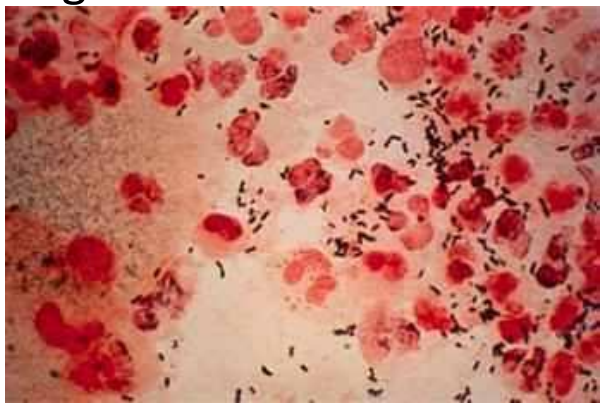
- Records of lab data with inconclusive history of viral hepatitis that may assist in making the donor eligibility determination include alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or prothrombin time.
  - If those tests are abnormal but a cause other than viral hepatitis was established, the donor may be eligible.

STI Clinical Evidence

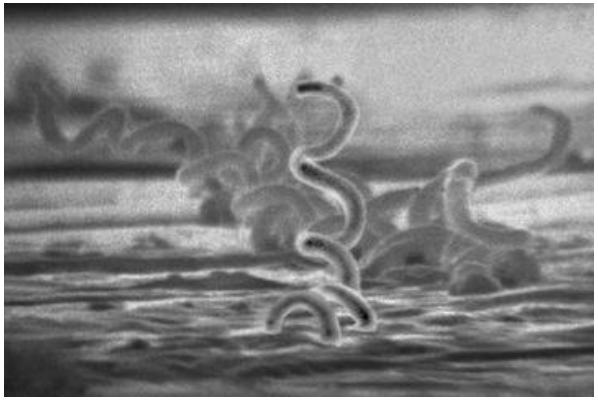
DE Guidance, IV.F.3.

Syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae* infection (screening and donor deferral for chlamydia and gonorrhea required only for donors of reproductive HCT/Ps):

- Persons who have had or have been treated for syphilis, chlamydia, or gonorrhea in the preceding 12 months
- Donors who were treated for the above more than 12 months ago may be eligible if evidence is presented that treatment occurred more than 12 months ago and was successful



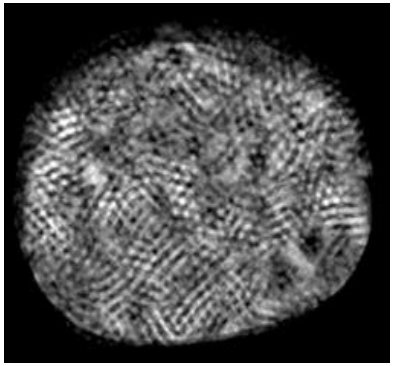
http://www.gonorrhea-symptoms.org/resurse/pictures/GonorrheaBacteria3.jpg



http://i.livescience.com/images/i/000/015/004/iFF/Treponema_pallidum.jpg?1298922092

Vaccinia Clinical Evidence

DE Guidance, IV.F.4.



http://www.pnas.org/content/102/8/2772/F5.medium.gif

Vaccinia infection

- Recent smallpox vaccination;
- Eczema vaccinatum;
- Vesicular rash indicative of generalized vaccinia in a person who has had recent smallpox immunization or who is a contact of someone with recent smallpox immunization;
- Progressive necrosis in an area of vaccination consistent with vaccinia necrosum;
- Postvaccinial encephalitis; and/or
- Vaccinial keratitis

WNV Clinical Evidence

DE Guidance, IV.F.5.

WNV Infection

- Symptoms may be nonspecific, so consider in light of other information obtained about the donor in making the DE determination

http://www.idph.state.il.us/envhealth/mos_wnv.jpg

- Mild symptoms (e.g., rash, swollen lymph glands)
- Severe symptoms (e.g., encephalitis, meningitis, meningoencephalitis, acute flaccid paralysis)

Clinical Evidence

DE Guidance, IV.F.6.

Sepsis

- Includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock
- For deceased donors, if any of these conditions are specifically diagnosed in the medical records during a hospital stay immediately preceding death, you should determine the donor to be ineligible.
- If a living donor appears healthy, the donor usually does not need to be evaluated for sepsis.

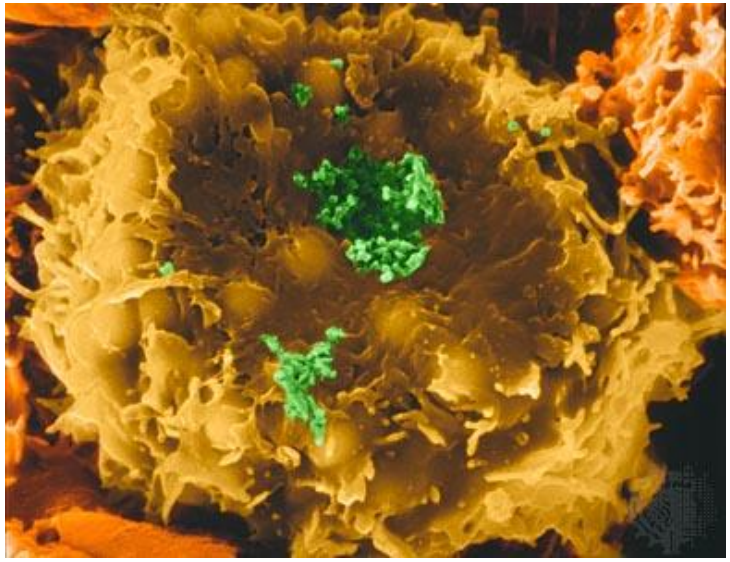
http://images.emedicinehealth.com/images/4453/4453-4482-12996-21147.jpg

Clinical Evidence

DE Guidance, IV.F.7.

HTLV infection (screening and donor deferral for HTLV required only for viable, leukocyte-rich HCT/P donors)

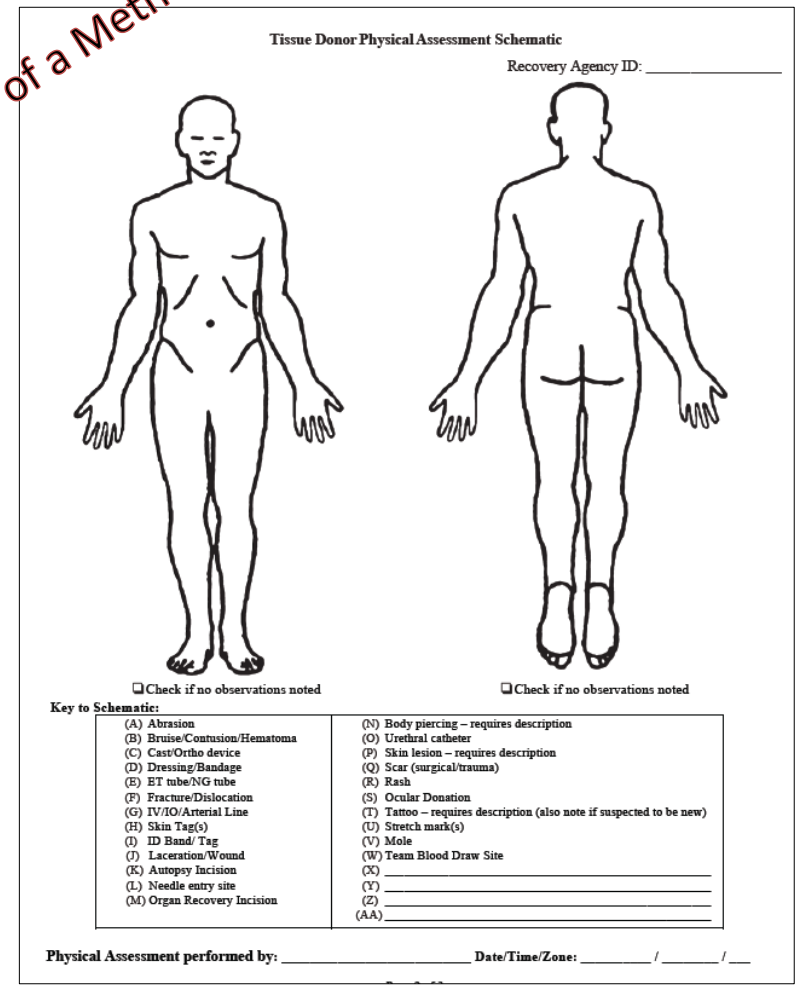
- Prior positive or reactive test for HTLV
- Unexplained paraparesis; and/or
- Adult T-cell leukemia



http://www.britannica.com/EBchecked/topic/275916/human-T-cell-lymphotropic-virus-type-I

PHYSICAL EVIDENCE

Example of a Method



Tissue Donor Physical Assessment Schematic

Recovery Agency ID: _____

❑ Check if no observations noted

❑ Check if no observations noted

Key to Schematic:

(A) Abrasion	(N) Body piercing – requires description
(B) Bruise/Contusion/Hematoma	(O) Urethral catheter
(C) Cast/Ortho device	(P) Skin lesion – requires description
(D) Dressing/Bandage	(Q) Scar (surgical/trauma)
(E) ET tube/NG tube	(R) Rash
(F) Fracture/Dislocation	(S) Ocular Donation
(G) IV/IO/Arterial Line	(T) Tattoo – requires description (also note if suspected to be new)
(H) Skin Tag(s)	(U) Stretch mark(s)
(I) ID Band/ Tag	(V) Mole
(J) Laceration/Wound	(W) Team Blood Draw Site
(K) Autopsy Incision	(X) _____
(L) Needle entry site	(Y) _____
(M) Organ Recovery Incision	(Z) _____
	(AA) _____

Physical Assessment performed by: _____ **Date/Time/Zone:** _____ / _____ / ___

Appendix III Donor Physical Assessment Form Requirements, 14th edition, AATB Standards for Tissue Banking

Physical Evidence

DE Guidance, IV.G.

Relevant medical records include the report of the ***physical assessment*** of a cadaveric donor or the ***physical examination*** of a living donor (§§ 1271.3(o), 1271.3(s))

- You should review the records of the physical assessment or physical examination for any of the following signs that may indicate high-risk behavior for or infection with a RCDAD.
- Some of the following are not physical evidence of HIV, hepatitis, syphilis or vaccinia, but rather are indications of high-risk behavior associated with these diseases and would increase the donor's relevant communicable disease risk.
- Except as noted in this section and in accordance with §1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following examples of physical evidence of RCDAD or high-risk behavior associated with these diseases.

Physical Evidence (Continued)

DE Guidance, IV.G.

1. Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, chancroid
   - Consider these signs in light of other information obtained about the donor

Physical Evidence (Continued)

DE Guidance, IV.G.

2. Physical evidence for risk of or evidence of syphilis
3. Male donors – physical evidence of anal intercourse including perianal condyloma

medicine.ucsd.edu

Physical Evidence (Continued)

DE Guidance, IV.G.

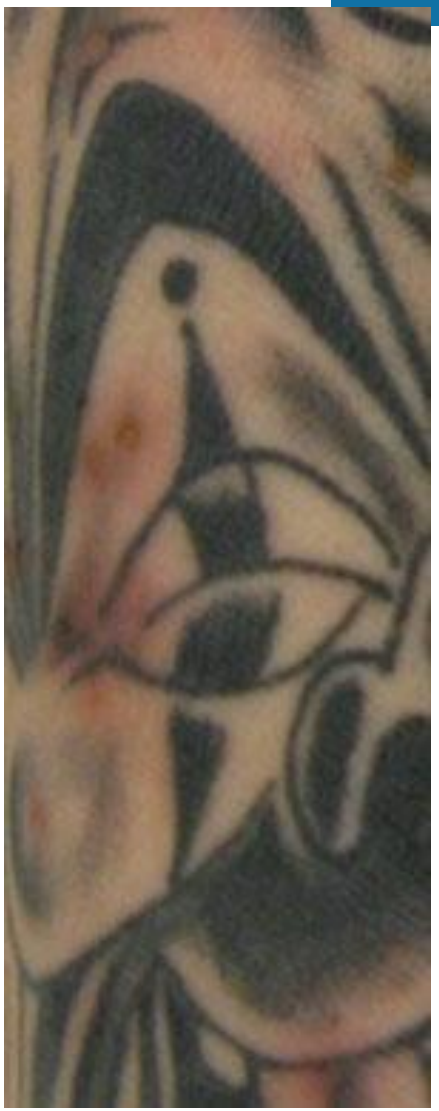
4. Physical evidence of nonmedical percutaneous drug use such as needle tracks
   - Examination should specifically include examination of tattoos, which might be covering needle tracks

http://deep6inc.com/images/heroin/her06-1.jpg

Physical Evidence (Continued)

DE Guidance, IV.G.

5. Physical evidence of recent tattooing, ear piercing, or body piercing in the preceding 12 months, in which sterile procedures were not used or instruments that have not been sterilized between uses were used



http://wwwnc.cdc.gov/eid/article/17/9/10-2011_article

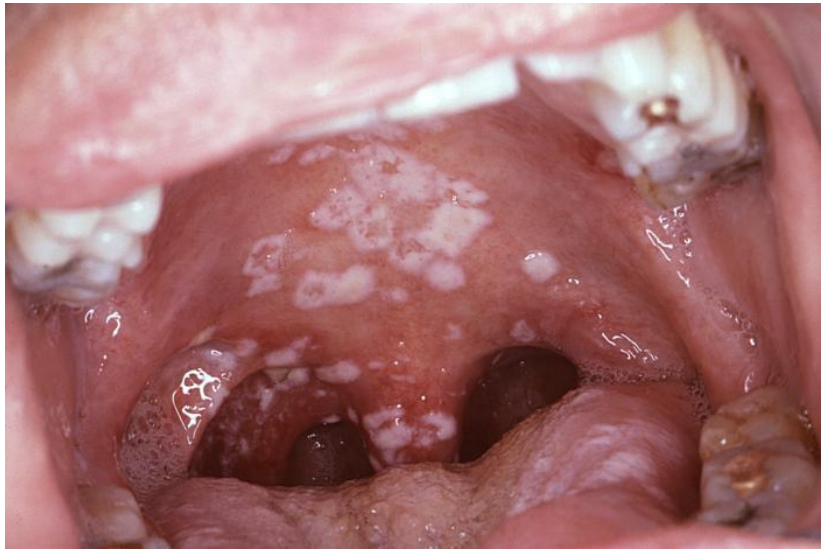
http://healthfoxx.com/wp-content/uploads/2013/04/Infected-Belly-Button-Piercing-Pictures.jpg

Physical Evidence (Continued)

DE Guidance, IV.G.

6. Disseminated lymphadenopathy
7. *Unexplained* oral thrush
8. Blue or purple spots c/w Kaposi's sarcoma

http://www.idoj.in/articles/2012/3/2/images/IndianDermatolOnlineJ_2012_3_2_135_96716_u1.jpg



http://hardinmd.lib.uiowa.edu/pictures22/cdc/6053_067_lores.jpg

Physical Evidence (Continued)

DE Guidance, IV.G.

9. *Unexplained* jaundice, hepatomegaly, or icterus (hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed)
10. Physical evidence of sepsis, such as *unexplained* generalized rash or fever

http://www.md-health.com/images/10420514/yellow-skin.jpg

http://images.emedicinehealth.com/images/4453/4453-4482-12996-21147.jpg

Physical Evidence (Continued)

DE Guidance, IV.G.

11. Large scab c/w recent history of smallpox immunization

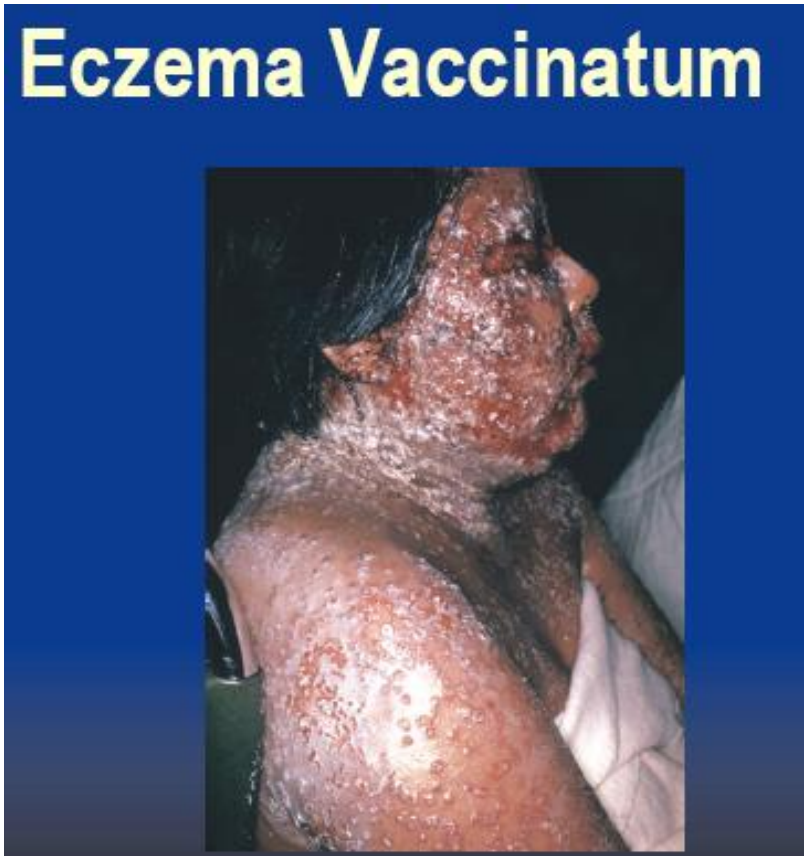
http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/

http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/

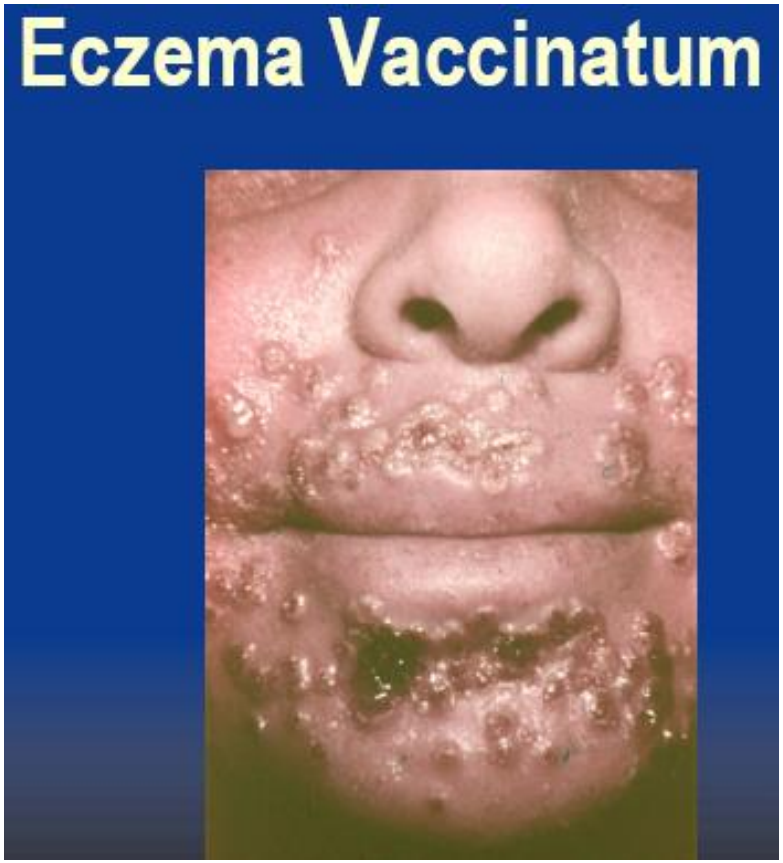
Physical Evidence (Continued)

DE Guidance, IV.G.

12. Eczema vaccinatum (seen in vaccinia)



http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/



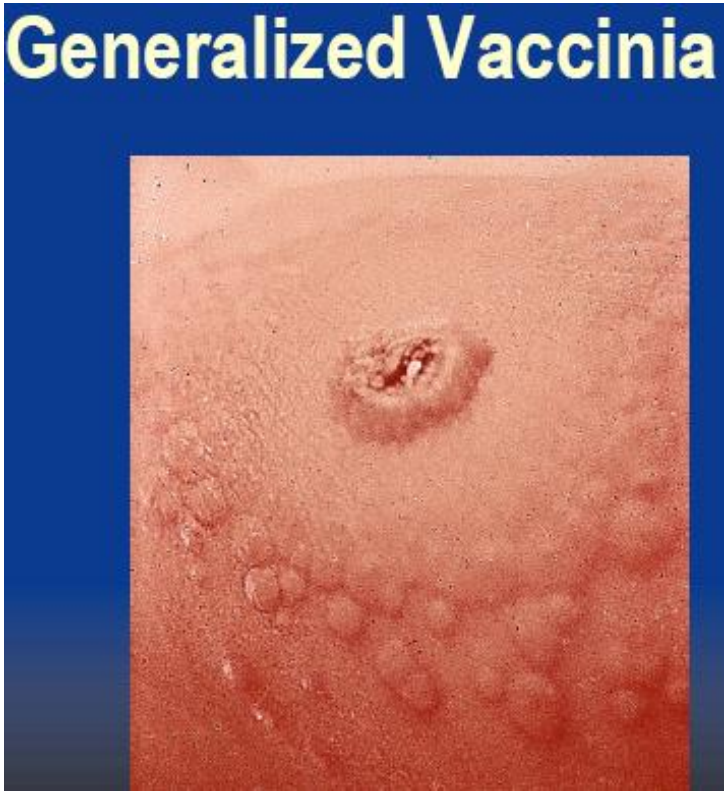
http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/

Physical Evidence (Continued)

DE Guidance, IV.G.

13. Generalized vesicular rash (generalized vaccinia)

http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/



http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/

Physical Evidence (Continued)

DE Guidance, IV.G.

14. Severely necrotic lesion c/w vaccinia necrosum

http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/

Physical Evidence (Continued)

DE Guidance, IV.G.

15. Corneal scarring c/w vaccinial keratitis

http://www.bt.cdc.gov/agent/smallpox/training/012403mmwr-slideset/

Q&A #3

Q3: If a male donor has genital warts on physical examination, is the donor ineligible according to FDA guidance, or can a responsible person make this decision?

http://www.mayoclinic.org/diseases-conditions/genital-warts/multimedia/male-genital-warts/img-20007073

Q&A #3

A3: The responsible person can make this decision. In the DE guidance, perianal condyloma (warts) is listed as a physical evidence finding for which a donor would be found ineligible, but genital warts are not. The establishment may choose its own policy related to genital warts. Perianal warts in men is a high risk finding because it *suggests* MSM behavior, which is an HIV risk factor.

Q&A #4

Q4: Does FDA have requirements regarding the timing (relative to the HCT/P recovery) of the physical exam? How often should a physical exam be performed on repeat donors?

Q&A #4

A4: No. FDA regulations only indicate that the exam be current – that should be defined in an establishment's SOPs. However, for repeat donors, a physical exam would need to be performed prior to the first donation, and the repeat donor would need a complete donor screening (including physical exam) at least once every 6 months. For non-repeat donors, donor screening (including the physical examination) must be complete prior to making a DE determination and distributing the HCT/Ps.

Summary

In this lesson, you learned about:

- The criteria for determining when donor screening is conducted

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=ae1deecc79a9f185d48af015ae277f5d&mc=true&tpl=/ecfrbrowse/Title21/21cfr1271_main_02.tpl

Tissue Guidances – Complete Listing
https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances

Searchable Guidances
https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

References

Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf

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
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf

Guidance for Industry: 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
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM529537.pdf

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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