FDA and the New Paradigm for Tissue Regulation

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FDA's Donor Eligibility Draft Guidance

Ellen Lazarus, M.D.
Director Regulatory Review
Division of Human Tissues
Office of Cellular, Tissue and
Gene Therapies

Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

- Published May 25, 2004 with DE Final Rule (69 FR 29835)
- Docket # 2004D-0193
- Comments currently under consideration

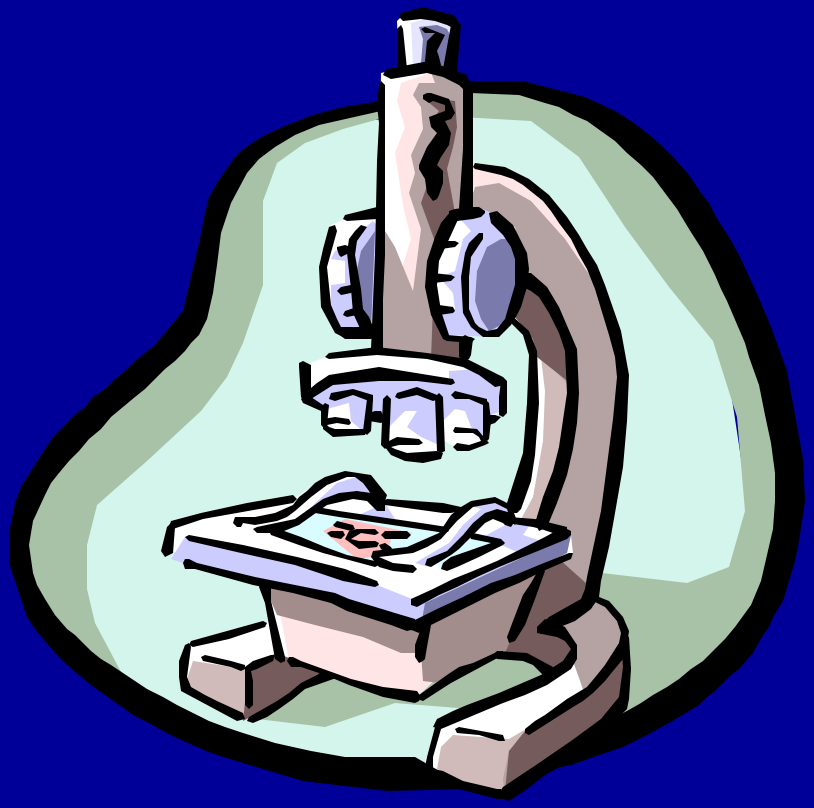
Purpose

- To provide recommendations for complying with the requirements in 21 CFR 1271, Subpart C
- Applies to HCT/Ps procured on or after May 25, 2005
- Does not replace 1997 Guidance, which applies to cells and tissues procured prior to May 25, 2005
- Finalize together with CJD guidance in one final guidance

Specific recommendations for compliance with DE rule

- Reviews criteria for determining that an emerging infectious disease is “relevant”
  - Provides public notice of our intention to add agents to the list of RCDADs; allows comments to the docket
  - Explains why FDA believes the standards for identification of a relevant communicable disease agent or disease have been met
- Describes specific risk factors, clinical evidence, physical evidence to use in donor screening
- Lists recommended donor screening tests

Additional Relevant Communicable Diseases and Disease Agents



- DE rule provides criteria for determination that a communicable disease agent or disease is “relevant” (21 CFR 1271.3(r))
- FDA will notify public in guidance if disease no longer “relevant”

“FDA believes that the following meet the standards for identification of relevant communicable disease agent”:

- West Nile Virus
- Sepsis
- Vaccinia (Smallpox vaccination)
- Severe Acute Respiratory Syndrome (SARS)

West Nile Virus (WNV)

Risk of transmission

- Potentially transmissible by an HCT/P
  - Has been transmitted by organ transplant, blood product transfusion, possibly breastfeeding, and from mother to fetus
- Sufficient incidence and/or prevalence in the potential donor population
  - From 1999 to 2003, ever increasing spread of infection throughout the U.S.

Severity of disease

- 80% asymptomatic; 20% flu-like symptoms
- 1 in 150 encephalitis, meningitis, paralysis
- 1 in 1000 infected persons die

WNV (criteria cont.)

Availability of screening measures

- Medical history interview, medical records review; donor is ineligible if:
  - Fever and headache simultaneously in past 7 days
  - Diagnosis of WNV in past 28 days or resolution less than 14 days prior to donation, whichever is the later date

Availability of tests for donor screening

- No licensed blood donor or cadaveric donor screening test
- NAT testing for living and cadaveric donors investigational

Screening for WNV

- Mild symptoms (non-specific)
  - Fever, headache, body aches, eye pain, skin rash, or swollen lymph nodes
- Severe illness
  - Encephalitis, meningitis, meningoencephalitis, acute flaccid paralysis
  - Headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness/paralysis

Sepsis

Bacteremia, septicemia, sepsis syndrome, systemic infection, septic shock

Risk of transmission

- Potentially transmissible by an HCT/P
  - Gram-positive and gram-negative bacteria and fungi have been transmitted by HCT/Ps
- Sufficient incidence and/or prevalence in the potential donor population
  - Incidence and prevalence of sepsis is increasing
  - Sepsis is among top 10 leading causes of death

Severity of disease

- Mortality is substantial (18-29%)

Sepsis (cont.)

- Availability of screening measures and tests
  - Medical history interview, medical record review, physical assessment (e.g. rash)
  - If medical records reveal bacteremia, septicemia, sepsis syndrome, systemic infection, or septic shock, donor is ineligible
  - Consider other systemic features (e.g. fever, heart rate, respiratory rate, WBC count, positive blood cultures, hypotension)

Screening for Sepsis

- Clinical infection and two or more of following
  - Temperature >100.4F (>38C)
  - Heart rate >90 beats/min
  - Respiratory rate >20 breaths/min or $PaCO_2$ <32
  - WBC <4000, >12,000, or >10% immature forms
- Positive (pre-mortem) blood cultures
- Unexplained rash
- Severe unexplained hypoxemia, elevated lactate, oliguria, altered mentation, hypotension

Vaccinia (Smallpox vaccine)

Risk of transmission

- Potentially transmissible by HCT/P
  - Viremia detected by two investigators when more virulent strain was used; needs further study
  - Virus can be recovered from vaccination site up to 18 days (mean 7.8 days—can be spread to other body parts and to close contacts)
- Sufficient incidence and/or prevalence in the potential donor population
  - Since Dec. 2002, when vaccination campaign began, targeted to those with an occupational risk, more than 600,000 people have been vaccinated by DoD

Screening for Vaccinia

- Recent smallpox vaccination
  - No complications
    - Defer donor until the scab has separated spontaneously, or for 21 days post-vaccination, whichever is later; if scab was removed before spontaneous separation, defer for 2 months after vaccination
    - For a cadaveric donor , if unable to determine how scab fell off, eligible if at least 21 days post-vaccination and no visible scab (cadaveric donor)

Vaccinia Screening, cont.

- Recent smallpox vaccination, with complications—defer until 14 days after resolution
  - Eczema vaccinatum—person with eczema
  - Generalized vaccinia—vesicular rash
  - Progressive vaccinia (vaccinia necrosum)—person with cell immunodeficiency
  - Postvaccinial encephalitis
  - Vaccinial keratitis—self-innoculation of eye

Vaccinia Screening (cont.)

- Close contact with vaccine recipient
  - Eligible if no skin lesion or other complication
  - If scab is present, defer
  - If scab was present but no longer present
    - Donor is eligible if scab separated spontaneously
    - Donor is deferred for 3 months if scab removed before spontaneous separation
  - Severe complications—defer until 14 days after resolution

Severe Acute Respiratory Syndrome (SARS) - during outbreaks

- Potentially transmissible by an HCT/P
  - Travel to outbreak areas within 10 days or close contact with person with SARS
    - Potential for transmission by HCT/Ps uncertain
    - Virus isolated from kidney, lung, BAL fluid
    - One case of virus detected by NAT in blood
    - Potential for viremia before sx or after resolution
- Sufficient incidence/prevalence during outbreaks
  - Only 8 confirmed cases and no spread in U.S. in 2003; coordinated public health response

SARS (cont.)

Availability of screening measures

- Medical hx interview to determine travel history, medical records review--**only when CDC lists SARS-affected areas on their website and person-to-person transmission is occurring
- Donor ineligible if SARS suspected or known, or treated in past 28 days
  - Close contact in past 14 days
  - Traveled to or resided in SARS-affected areas in past 14 days
  - www.cdc.gov/ncidod/sars/index.htm

Screening for SARS during outbreaks

- Asymptomatic/mild respiratory illness
  - Viremia has not been detected in asymptomatic persons; antibody has been detected
- Moderate respiratory illness
  - Temperature >100.4F (38C), and
  - Lower respiratory clinical findings (cough, shortness of breath, difficulty breathing, or hypoxia
- Severe respiratory illness
  - Temperature as above, and
  - Clinical findings as above, and
  - radiographic evidence of pneumonia or respiratory distress syndrome

Communicable disease risks from Xenotransplantation

Xenotransplantation—any procedure that involves the transplantation, implantation, or infusion of (1) live cells, tissues, or organs from a nonhuman animal; or (2) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs

Xenotransplantation (cont.)

Defer persons who are xenotransplantation product recipients or intimate contacts of xenotransplantation product recipients

- Intimate contact means a person who has engaged in activities that could result in intimate exchange of body fluids, including blood or saliva
  - Examples—sexual partners, household members who share razors or toothbrushes, healthcare workers with repeated percutaneous, mucosal, or other direct exposure

Compare this draft guidance with July 1997 Guidance

- For a donor who is one month of age or younger—screen both mother and infant
- Sex in the preceding 12 months with any person known or suspected of having HIV infection, clinically active HBV infection, or HCV infection
- Children born to mothers with or at risk for HIV infection, if 18 months of age or younger, or if breastfed within preceding 12 months
- Persons who have had acupuncture in the preceding 12 months are not deferred

Guidance Comparison (cont.)

- Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after age 11, unless evidence from the time of illness documents that the hepatitis was identified as hepatitis A (e.g., a reactive IgM anti-HAV test)
- Persons who have had or have been treated for syphilis or gonorrhea during the preceding 12 months. FDA recommends that, after 12 months, the donor may be re-entered after presenting evidence of successful treatment for syphilis.

Donor testing: Specific test recommendations

- HIV, type 1 (FDA-licensed screening test either for anti-HIV-1 or combination test for anti-HIV-1 and anti-HIV-2)
- HIV, type 2 (FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2)
- HBV (FDA-licensed screening test for HBsAg and for total antibody to anti-HBc)
  - Exception for cord blood collection and storage
- HCV (FDA-licensed screening test for anti-HCV)
- Treponema pallidum (FDA-cleared serologic test)
  - Exception for syphilis test results

Donor Testing: Other Recommendations

- Nucleic acid testing (NAT): Recommended for testing of living donors using FDA-licensed NAT blood donor screening tests for HIV and HCV
- p24 antigen tests: Not recommended
- "Nonrecommended" tests: Must be considered when you make a donor eligibility determination
- Confirmatory tests: Negative results would not override reactive screening test (except syphilis)
- Anti-HBs: Donor may be eligible in absence of other markers for Hepatitis B infection

Donor Testing: Triplicate testing

- Some HCT/P establishments rely solely on the test results obtained by an OPO.
- As described by CDC, an OPO may run an enzyme immunoassay initially in triplicate.
- If you rely solely on such triplicate test results, obtain the results of the three individual wells performed in a single run.
- Three nonreactive results in a single run would constitute a negative result. If any other results are obtained, the donor would not be eligible to donate HCT/Ps.

Plasma Dilution

- Blood loss includes blood lost within a body cavity or outside the body
- Autologous blood removed pre-operatively or peri-operatively and reinfused during the same surgical procedure would not need to be included in plasma dilution calculations
- A plasma dilution of >50% (1:2 dilution) could make test results unreliable
- Calculate BOTH blood volume and plasma volume and compare volumes infused over a period of time with BOTH.

Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by HCT/Ps

- Published June 2002
- Modeled after blood guidance
- Limited information available about risk reduction versus supply
- Plan to combine and publish with DE guidance

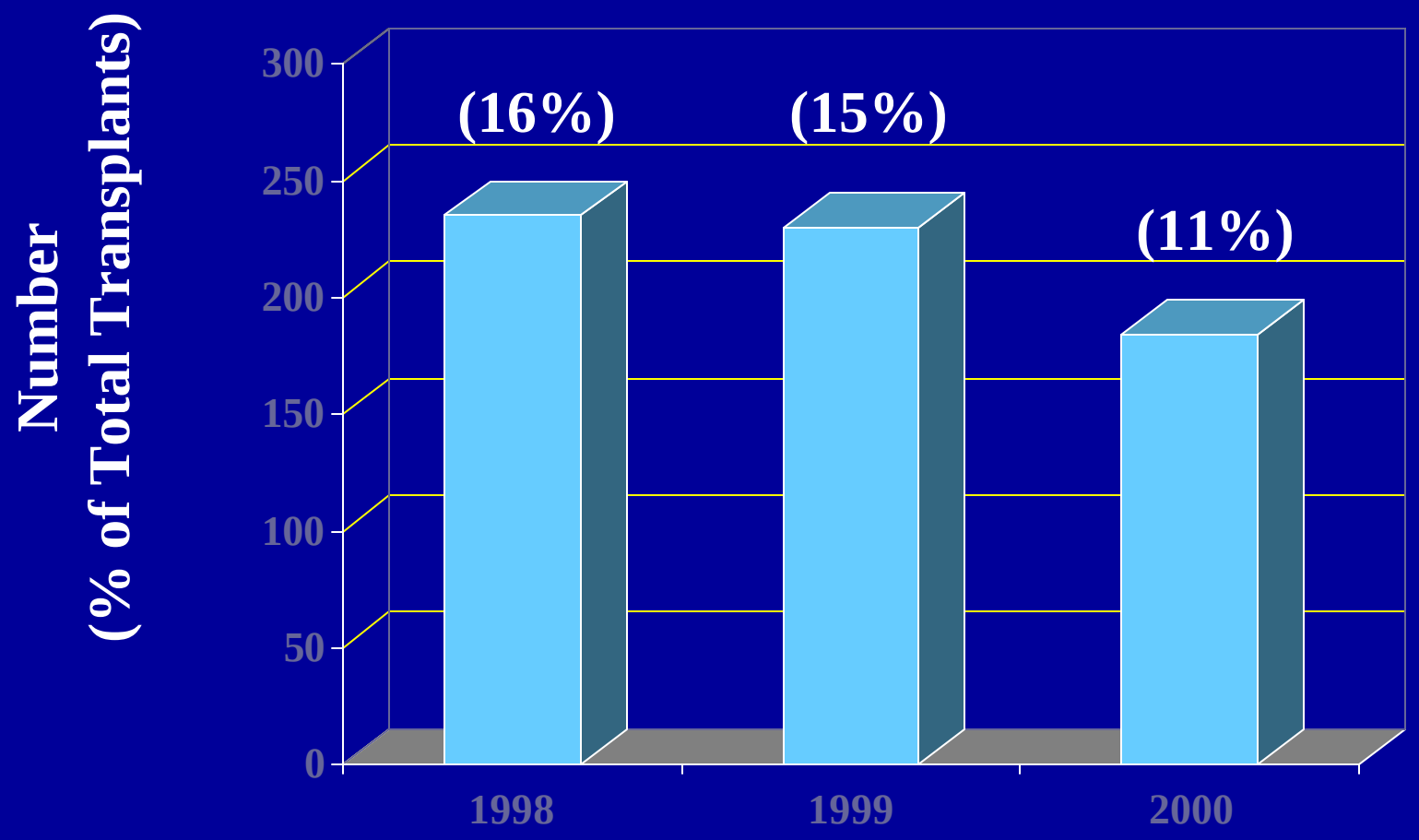
HCT/P CJD Draft Guidance Background

- January 2001 TSEAC Meeting
  - Unanimous agreement that there is a significant risk of transmission of vCJD from HCT/Ps as compared to the risk of vCJD from blood transfusion
    - Greatest risk: dura mater and cornea
    - No reason to believe risk of vCJD less than that for sporadic CJD

HCT/P CJD Draft Guidance Background (cont.)

- January 2001 TSEAC (cont.)
  - Majority agreement that FDA should recommend donor deferral criteria for possible exposure to the BSE agent
  - Exception for Hematopoietic Stem/Progenitor Cells (HPC) should be provided

Donors from Europe Providing HPC for U.S. Patients: 1998 - 2000



NMDP unpublished data, TSEAC 2001

HCT/P CJD Draft Guidance Background (Cont.)

- January 2001 TSEAC (Cont.)
  - No advice from committee regarding specific deferral criteria
    - Countries
    - Time periods of potential exposure
    - Duration of exposure

HCT/P CJD Draft Guidance

Determine ineligible any donor who:

1. Has been diagnosed with vCJD or any other form of CJD
2. Has been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system (CNS) or other neurological disease of unknown etiology
   - Donor with dementia may be acceptable based upon evaluation by the medical director if confirmed by gross and microscopic examination to be caused by CVA, brain tumor, head trauma, or toxic/metabolic and not by TSE)

HCT/P CJD Draft Guidance (cont.)

Determine ineligible any donor who:

3. Is at increased risk for CJD
   - Dura mater transplant recipient
   - Human pituitary-derived growth hormone
   - 1 or more blood relatives with CJD
4. Spent three months or more cumulatively in the U.K. from 1980 through end of 1996

HCT/P CJD Draft Guidance (cont.)

Determine ineligible any donor who:

5. Is a current or former U.S. military member, civilian military employee, or dependent of military or civilian employee who resided at U.S. military bases in Northern Europe for 6 months or more from 1980 through 1990, or at U.S. military bases elsewhere in Europe for 6 months or more from 1980 through 1996
6. Lived cumulatively for 5 years or more in Europe from 1980 until the present (including time spent in the U.K. from 1980-1996)

HCT/P CJD Draft Guidance (cont.)

Determine ineligible any donor who:

7. Received any transfusion of blood or blood components in the U.K. between 1980 and the present
8. Has injected bovine insulin since 1980, unless confirmed not manufactured after 1980 from cattle in the U.K.

HCT/P CJD Draft Guidance (cont.)

- All geographical references in the deferral recommendations are defined in the document: e.g. Northern Europe
- Recognition is given to HLA-matching issues with HPC
  - If a HPC donor would otherwise be determined ineligible by recommendations 3-8, the risks of using the cells may be outweighed by the benefits; the HPC product may be collected and stored
  - Use of the HPC product in this circumstance may be considered an “urgent medical need.”

HCT/P CJD/vCJD Draft Guidance (cont.)

- CJD/vCJD screening questions to be included in the donor's medical history.
- Unfamiliarity with term CJD may be taken as a negative response.
- CJD in blood relative excluded unless:
  - Diagnosis of CJD subsequently found inaccurate
  - The CJD was iatrogenic
  - Lab testing shows donor without mutation associated with familial CJD

Summary

- Currently reviewing comments to docket
- Plan to combine CJD/vCJD and draft DE guidance in single guidance document
- New donor testing technology for detecting emerging diseases and shorten window periods