Testing Donors of Human Cells and Tissues

2nd Annual FDA and the Changing Paradigm for Tissue Regulation

February 8, 2006

Las Vegas, Nevada

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Food and Drug Administration

100 YEARS 1902 2002 BIOLOGICS CONTROL ACT

FDA CBER Center for Biologics Evaluation and Research

Today's Discussion

- Donor Eligibility and RCDADs
- General information re: Donor Testing
- Diagnostic vs. Screening Test kits
- Donor Screening Tests
- Cadaveric Claims
- Organ and "other living donors"
- Specific issues to consider with HCT/P testing

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-lymphotrophic virus
- CMV = Cytomegalovirus
- §= Section (of the rule) ex. §1271.3
- PI = Package Insert ID = Individual Donor
- BV = Blood Volume PV = Plasma Volume
- CJD = Creutzfeldt-Jakob disease (vCJD=variant)
- NAT = Nucleic Acid Amplification Technology *or* "Nucleic Acid Test"—Polymerase Chain Reaction (PCR) and Transcription-Mediated Amplification (TMA)

Donor Eligibility and RCDADs

- Donor Eligibility rule defines relevant communicable disease agents or diseases (RCDADs); establishments must screen and/or test for RCDADs
- Defined in 1271.3(r) – (1) lists particular RCDADs and (2) describes when communicable disease agents or diseases may be added to the list of RCDADs – in order to allow additions based on emerging infectious diseases
- Additions to the "list" of RCDADs would be added through guidance (draft, public comment, then finalize, except in cases of public health emergency)

RCDADs

- For all HCT/Ps
  - HIV, types 1 and 2
  - HBV
  - HCV
  - Human TSE, including CJD
  - Treponema pallidum (agent of syphilis)
- For viable, leukocyte-rich HCT/Ps
  - HTLV, types I and II
- For reproductive HCT/Ps
  - Chlamydia trachomatis
  - Neisseria gonorrhea

Additional RCDADs

- The donor eligibility draft guidance adds new RCDADs according to definition in § 1271.3(r)(2) (published May 2004; not finalized)
- "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)

Donor Testing - General

- Donor testing must be performed at lab
  - Registered with FDA
  - CLIA certified or CMS equivalent
- Donor tests
  - FDA-licensed, approved, or cleared donor SCREENING tests (not diagnostic)
  - Used in accordance with the PI
  - Should be labeled for use for cadaveric donors if such a test is available (and appropriate)
  - Recommendations for specific tests may change with time and increasing technology

Donor Testing - General

- Performance and Interpretation of test results
  - ONLY according to manufacturer’s instructions in the Package Insert (PI)
  - Triplicate testing is NOT recommended in any manufacturer's test kit instructions
- Specimen collection should be at same time as, or within 7 days before or after, collection of the cells or tissues with certain exceptions
- Donors who have had transfusions or infusions 48 hours prior to specimen collection should be excluded unless you evaluate them for plasma dilution (algorithm included in guidance)

Screening vs Diagnostic test kits

- Clinical trials to support donor screening test kits perform testing in a “pre-screened”, low-prevalence population (emphasis on sensitivity)
- Clinical trials to support diagnostic test kits generally perform testing in a symptomatic population with suspicion of having a particular disease before the test is performed (more emphasis on specificity)
- Performance of a test kit in a low-prevalence population is generally not known (except for Chlamydia trachomatis and Neisseria gonorrhea) for diagnostic test kits

Screening vs Diagnostic test kits

- Diagnostic test kits are not required to be performed according to test kit manufacturer's instructions—modifications may be made as long as the lab validates the changes.
- FDA believes that tests specifically labeled for use for donor screening are the best tests to use in any donor screening situation

Donor Screening Tests

- Specifically recommended tests include FDA licensed (or cleared) screening tests for
  - HIV types 1 and 2 – anti-HIV-1 *and* anti-HIV-2 or licensed combination test
  - HBV – HBsAg *and* anti-HBcore (total=IgG+IgM)
  - HCV – anti-HCV
  - *Treponema pallidum* serological test for syphilis (Donor with reactive non-Treponemal screening test and nonreactive specific Treponemal confirmatory test is permitted to donate)

Donor Screening Tests

- Additional screening tests for viable, leukocyte-rich cells or tissue
  - HTLV types I and II – FDA-licensed anti-HTLV I/II
  - CMV – not RCDAD, but must test, using FDA-cleared screening test for anti-CMV.
- Additional tests for genitourinary diseases for donors of reproductive cells and tissues
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhea*
  - Currently no FDA-licensed, approved, or cleared donor *screening* tests for either. Use an NAT approved for diagnostic use

NAT and Donor Testing

- DE Draft Guidance published before any NATs were approved for use in cadaveric specimens; at that time only HIV and HCV were licensed for use in blood donor (or other living donors) screening
- Draft guidance states “As more information becomes available, FDA may recommend these tests for use in cadaveric tissue donors.”
- “FDA does recommend that living donors of HCT/Ps (e.g., hematopoietic stem/progenitor cell donors, semen donors) be tested with FDA-licensed NAT blood donor screening tests for HIV and HCV.”

Currently Licensed NAT test kits for donor screening

- Gen-Probe/Chiron – Procleix HIV-1/HCV Nucleic Acid Test (TMA); WNV [B, P, L/O, C]
- National Genetics Institute – UltraQual HIV-1 RT-PCR & HCV RT-PCR Assays [P]
- Roche Molecular Systems – COBAS AmpliScreen HIV-1; HBV; HCV Assays (PCR) [B, P, L/O, C]—separate assays
- B – Blood P – Plasma L/O - Other living donors and Organ donors C - Cadaveric

NAT Donor Screening in the Pipeline* (under IND)

- WNV – Roche Molecular Systems [B, P, C];
- HBV – Gen-Probe has HBV as part of multiplex test (Ultrio) under consideration for BLA at this time [B, P, L/O, C]

* Publicly available information, with knowledge of manufacturer

Cadaveric Indication (Claim)

- FDA considers cadaveric specimens to be different than blood donor specimens; additional validation studies must be performed by the test kit manufacturer to get this claim
- Claims for cadaveric specimen testing may be obtained as an additional claim (or supplement on already approved test) for tests with an indication for use in screening blood donors
- ’95-Letters to test-kit manufacturers—minimum protocol
- Guidance published November 2004 “Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)”
- FDA works with industry to encourage development of tests for use with cadaveric blood specimens
- Least Burdensome Approach

Minimal study requirements for cadaveric indication

- Studies – sensitivity, specificity, reproducibility
- May do studies of matched pairs of pre- and post-mortem specimens OR spiking studies (approach we have seen) using spiked cadaveric specimens (at a potency near the assay's cutoff) + spiked unmatched pre-mortem specimens
- Minimum of 50 specimens for sensitivity and specificity studies; 20 specimens for reproducibility

Minimal study requirements for cadaveric indication

- Minimum of 3 test kit lots for each study
- Plasma dilution must be taken into consideration
- Additional information about donors of the cadaveric specimens:
  - Time between death and specimen collection; how/where specimen was collected
  - Use hemolyzed specimens, note degree of hemolysis
  - Note information about storage and handling conditions of the specimens

Donor Screening Serology Tests with Cadaveric Indication

- Abbott Laboratories: Auszyme EIA for HBsAg; HCV EIA 2.0; and Abbott HIVAB HIV-1/HIV-2 (rDNA) EIA
- Bio-Rad Laboratories: Genetic Systems EIA for HBsAg; Genetic Systems HIV-1/HIV-2 Peptide EIA; Genetic Systems HIV 1/HIV-2 Plus O EIA

HCT/P Testing Issues

- Notable issues with HCT/P specimens
  - No validation of testing after long term specimen storage (this would be very helpful to the HCT/P industry)
  - Claims for HCT/P donors may only use individual donor (ID) testing and not be pooled testing unless separate validation is performed by the test kit manufacturer (none to date)
  - Turnaround time is often an issue with cadaveric HCT/Ps – e.g., corneas, skin
  - It is helpful to have claims to collect specimens in both serum and plasma tubes for cadaveric specimens because of limited specimen volume

Organ and "other living donors"

- "The Procleix® WNV Assay is a qualitative in vitro nucleic acid assay system for the detection of West Nile Virus (WNV) RNA in plasma specimens from individual human donors, including volunteer donors of whole blood and blood components, *and other living donors*. It is also intended for use in testing plasma specimens to screen *organ donors when specimens are obtained while the donor's heart is still beating*, and in testing blood specimens to screen cadaveric (non-heart-beating) donors. It is not intended for use on cord blood specimens."

Organ and "other living donors"

- "…The assay is intended for use in testing individual donor samples. It is also intended for use in testing pools of human plasma comprised of equal aliquots of not more than 16 individual donations *from volunteer donors of whole blood and blood components*.
- This assay is not intended for use as an aid in the diagnosis of West Nile Virus infection."

Organ and “other living donors”

- The organ/other living donor indication for use does not require data submission—manufacturers need only request the additional language
- This indication with its descriptive language was developed to improve access to the NAT tests. With previously licensed NAT tests, the indications for use were written differently and were more restrictive in the language—some donor populations had difficulty accessing the tests (e.g., human milk donors)
- *Individual Donor (ID) testing only* (unless data is submitted by test kit manufacturer to pool samples from several donors and then test the “minipool” —none to date)

Organ donor testing

- FDA does not regulate organ transplantation; nor do we decide what screening and testing should be performed for organ donors
- The risk/benefit ratio for HCT/Ps and organs is different – as such, organ donor screening and testing are different
- Further information is contained in the OPTN policies at: http://optn.org/PoliciesandBylaws/policies/pdfs/policy_2.pdf

Donor Testing Points to Consider

- Work with your testing laboratory (FDA-registered and CLIA-certified/equivalent) to assure that the lab is using the proper test for your situation:
  - Is it FDA-licensed, cleared, or approved for donor screening purposes?
  - Is it approved for cadaveric specimens?
  - What kind of specimen does the test require?
  - Should the test be performed using individual donor (ID) specimens or is the use of pooled specimens acceptable?
  - What specimen storage/handling requirements should you consider?
- Examples of each issue on the following slides

Is the test approved for donor screening purposes?

- **Vironostika® HIV-1 Plus O Microelisa System (Biomérieux)**
- **Intended Use:** The Vironostika® HIV-1 Plus O Microelisa System is an enzyme-linked immunosorbent assay (ELISA) for the qualitative detection of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1), including Group O, in human specimens collected as serum, plasma, or dried blood spots. The Vironostica HIV-1 Plus O Microelisa System is intended for use as an aid in diagnosis of infection with HIV-1. It is not intended for use in screening blood donors.

Is the test approved for donor screening purposes?

- **Anti-HBc Reagent Pack** (*Vitros* Immunodiagnostic Products)
- **Intended Use**: For the *in vitro* qualitative detection of total antibody (IgG and IgM) to hepatitis B core antigen (total anti-HBc) in human adult and pediatric serum and plasma (EDTA and citrate) …Assay results, in conjunction with other serological and clinical information, may be used for the laboratory diagnosis of individuals with acute or chronic hepatitis B, or recovery from hepatitis B infection…**WARNING: This assay has not been FDA cleared or approved for the screening of blood or plasma donors.**

Is the test approved for donor screening purposes?

- **HIVAB HIV-1/HIV-2 (rDNA) EIA** (Abbott Laboratories)
- HIVAB HIV-1/HIV-2 (rDNA) EIA is an *in vitro* enzyme immunoassay for the qualitative detection of antibodies to human immunodeficiency viruses type 1 and/or type 2 (HIV-1/HIV-2) in human serum, plasma, or cadaveric serum.
- Original approval date 2/1992 (cadaveric supplement submitted later)
- Listed on CBER website as “Donor Screen”

Is the test approved for donor screening purposes?

- **COBAS AmpliScreen™ HIV-1 Test, version 1.5** (Roche Molecular Systems)
- **Intended Use:** The COBAS AmpliScreen™ HIV-1 Test…is a qualitative in vitro test for the direct detection of…HIV-1 RNA in human plasma. [It] is intended to be used for detection of HIV-1 RNA in conjunction with licensed tests for detecting antibodies to HIV-1. This product is intended for use as a donor screening test to detect HIV-1 RNA in plasma samples from individual human donors, including donors of Whole Blood and blood components, Source Plasma and other living donors.

Is the test approved for donor screening purposes?

- …It is also intended for use to screen organ donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on specimens from cadaveric (non-heart-beating) donors. This test is not intended for use on samples of cord blood. This test is not intended for use as an aid in diagnosis…

Is the test approved for donor screening purposes?

- Generally “newer” test kits are clearly labeled with (or without) the donor screening indication
- Donor screening tests are regulated by CBER

http://www.fda.gov/cber/products/testkits.htm

- Except for retroviruses (HIV and HTLV) diagnostic tests regulated by CBER, other diagnostic tests are regulated by CDRH

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfivd/index.cfm

- If you are in doubt, you can ask CBER!

Is the test approved for cadaveric specimens?

- **HIVAB HIV-1/HIV-2 (rDNA) EIA** (Abbott Laboratories)
- **Intended Use Statements:** HIVAB HIV-1/HIV-2 (rDNA) EIA is an *in vitro* enzyme immunoassay for the qualitative detection of antibodies to human immunodeficiency viruses type 1 and/or type 2 (HIV-1/HIV-2) in human serum, plasma, or cadaveric serum.

Is the test approved for cadaveric specimens?

- **COBAS AmpliScreen™ HIV-1 Test, version 1.5** (Roche Molecular Systems)
- **Intended Use Statements:** …It is also intended for use to screen organ donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on specimens from cadaveric (non-heart-beating) donors. This test is not intended for use on samples of cord blood. This test is not intended for use as an aid in diagnosis…
- But newer version has a cadaveric claim

Is the test approved for cadaveric specimens?

- Newer labeling is clear when something is NOT labeled for cadaveric specimens
- If the indications for use section does not explicitly mention cadaveric specimens, then you should assume the test is NOT approved for use with cadaveric specimens
- If you are testing specimens from living donors OR if you are testing pre-mortem specimens (even if the donor is deceased), you are not required to use a test with an additional indication for use in cadaveric specimens

What kind of specimen does the test require?

- **Genetic Systems™ HIV-1/HIV-2 *Plus O* EIA** (Bio-Rad)
- **Intended Use**: …for the detection of antibodies to HIV-1 (Groups M and O) and/or HIV-2 in human serum, plasma, and cadaveric serum specimens. It is indicated as a screening test for serum, plasma, and cadaveric serum specimens and as an aid in the diagnosis of infection with HIV-1 and/or HIV-2.

What kind of specimen does the test require?

- **Specimen Collection, Preparation, and Storage:** Serum, plasma, or cadaveric serum specimens may be used in the test. The following anticoagulants, including those in both glass and plastic tubes, have all been evaluated and found to be acceptable: EDTA, sodium and lithium heparin, sodium citrate, CPT, CPDA-1, and ACD. Samples that are collected into anticoagulant tubes should be filled as labeling indicates to avoid improper dilution…

What kind of specimen does the test require?

- **Procleix® HIV-1/HCV Assay** (Gen-Probe and Chiron)
- **Intended Use:** …for the detection of [HIV] type 1 and/or hepatitis C virus RNA in human plasma specimens from individual blood donors, including donors of whole blood and blood components, source plasma and other living donors. It is also intended for use in testing plasma to screen organ donors when specimens are obtained while the donor's heart is still beating, and from blood specimens from cadaveric (non-heart-beating donors)….

What kind of specimen does the test require?

- **Specimen Collection, Storage and Handling:**
- Living Donor Blood Specimens A. Plasma collected in glass or plastic tubes may be used. B. Plasma collected in K_2EDTA, K_3EDTA or in Becton-Dickinson EDTA Plasma Preparation Tubes (PPT) may be used…
- Cadaveric Blood Specimens A. Cadaveric blood specimens can be collected in clot or anticoagulant tubes.

What kind of specimen does the test require?

- General information about the specimen type can be found in the intended use statements
- More detailed information about the specimen type is generally found in a “Collection, Storage and Handling” (or similar) section
- Only use the specimen types in accordance with the package insert – could otherwise yield invalid results and would be a regulation violation because you must follow the test kit manufacturer’s instructions when performing donor screening tests

Should the test be performed using individual donor specimens or are pooled donor specimens acceptable?

- **Genetic Systems™ HIV-1/HIV-2 *Plus O* EIA** (Bio-Rad)
- **Intended Use**: …for the detection of antibodies to HIV-1 (Groups M and O) and/or HIV-2 in human serum, plasma, and cadaveric serum specimens. It is indicated as a screening test for serum, plasma, and cadaveric serum specimens and as an aid in the diagnosis of infection with HIV-1 and/or HIV-2.

ID Testing vs Pooled?

- **COBAS AmpliScreen HIV-1 Test, version 1.5** (Roche Molecular Systems)
- **Intended Use:** …Plasma from all donors may be screened as individual samples. For donations of Whole blood and blood components, plasma may be tested in pools comprised of equal aliquots of not more than 24 individual donations. For donations of Source Plasma, plasma may be tested in pools comprised of equal aliquots of not more than 96 individual donations.
- *Pools only mentioned for types of products above; therefore, pooling is not acceptable for other living donors, organ donors, or cadaveric donors*

ID Testing vs Pooled?

- **Procleix® HIV-1/HCV Assay** (Gen-Probe and Chiron)
- **Intended Use:** …The assay is intended for use in screening individual donor samples of all specimen types, or pools of human plasma comprised of equal aliquots of not more than 16 individual donations for donors of whole blood, blood components, or source plasma. This assay is intended to be used in conjunction with licensed tests for detecting antibodies to HIV-1 and HCV.

What specimen storage/handling requirements to consider?

- **HCV EIA 2.0** (Abbott Laboratories)
- **Specimen Collection and Preparation**
  - 6. Serum or plasma specimens may be stored for up to 14 days at 2 to 8°C. However, if storage periods of greater than 14 days are anticipated, the specimens should be stored frozen at -10 °C or colder.
  - 7. Cadaveric serum specimens may be stored for up to five days at 2 to 8°C. However, if storage periods of greater than five days are anticipated, the specimens should be stored frozen at -20°C or colder.

What specimen storage/handling requirements to consider?

- 12. If serum or plasma specimens are to be shipped…Specimens may be shipped ambient, refrigerated (2 to 8°C) on wet ice, or frozen (-10 °C or colder) on dry ice…
- 13. If cadaveric serum specimens are to be shipped…Cadaveric serum specimens may be shipped refrigerated (2 to 8°C) on wet ice or frozen (-10 °C or colder) on dry ice…

What specimen storage/handling requirements to consider?

- The package insert has useful information, including
  - Shipping temperatures
  - Storage temperatures
  - How soon after specimen drawn that the test must be performed
  - Proper specimen containers
- Testing laboratories should be able to help you develop SOPs for how to collect, store and ship specimens for whatever donor testing you need to perform

Any Questions?

Further Information

- Cadaveric guidance located at http://www.fda.gov/cber/gdlns/cadbldhctp.pdf
- Cadaveric claims are jointly reviewed by OCTGT and OBRR
- All tissue related publications can be found at http://www.fda.gov/cber/tissue/docs.htm
- CBER-approved donor screening test kits

  http://www.fda.gov/cber/products/testkits.htm
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