Update of NAT screening policy in the US

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DETTD/CBER/FDA

XXIII SoGAT meeting
HIV-1 and HCV NAT

1. FDA licensed HIV-1 and HCV NAT in 2001 for testing pools of plasma from Source Plasma donors and in 2002 for Whole Blood collections.

2. NAT is included in screening of all donations of Whole Blood and blood components (including Source Plasma and Source Leukocytes) in addition to an FDA licensed HIV antibody test and HCV antibody test.
HIV-1 and HCV NAT – cont.


4. NAT standard for licensure was 100 IU/ml for the pool test for both HIV-1 and HCV.

5. HIV-1 p24 antigen testing was discontinued on implementation of NAT approved to replace this test.
HIV-1/HCV NAT

- HIV-1/HCV NAT Final guidance on testing and re-entry issued May 2010

- NAT algorithms for testing, re-entry of 3 groups of donors deferred because of HIV test results
Testing, Product Disposition, Donor Mgmt., Lookback for **Multiplex HIV-1/HCV MP-NAT Reactive** or **ID-NAT Reactive**

**MP-NAT Reactive:**
Resolve by Testing Subpools

**TEST INDIVIDUAL REACTIVE DONOR SAMPLES USING SAME MULTIPLEX NAT METHOD**

**ID-NAT Reactive:**
- Reactive Donor Sample(s)
- Non-Reactive Donor Samples

**TEST USING DISCRIMINATORY NAT(s).**

**RELEASE**
TEST USING DISCRIMINATORY NAT(s).

<table>
<thead>
<tr>
<th>Reactive for HIV-1 and/or HCV</th>
<th>Non-Reactive for both HIV-1 and HCV (Non-Discriminated Reactives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESTROY or RELABEL UNIT.</td>
<td>DESTROY or RELABEL UNIT.</td>
</tr>
<tr>
<td>DEFER and NOTIFY DONOR.</td>
<td>DEFER DONOR for 6 MONTHS, REENTER</td>
</tr>
<tr>
<td>PERFORM LOOKBACK</td>
<td>without TESTING SAMPLE.</td>
</tr>
<tr>
<td>for HIV-1 and/or HCV.</td>
<td>NOTIFY DONOR: “Likely FP, Not Infected.”</td>
</tr>
<tr>
<td>Donor Eligible for Reentry.</td>
<td>PERFORM LOOKBACK for HIV-1 and HCV.</td>
</tr>
</tbody>
</table>

(VARIANCES)
Advances in HIV Tests
Used as an Aid in Diagnosis

FDA has approved:

- Tests that use urine and oral fluid
- Automated assay platforms and NAT
- 2 Over-the-Counter Anti-HIV-1 Testing Services
  - Use dried blood spots / mail
- 8 Rapid HIV-1 Antibody Tests
  - 1 gives a result in 1 minute!
  - Use finger-stick blood, oral fluid, etc.
- An Antibody/Antigen “combo” assay
Advances in HIV Tests Used for Monitoring Therapy

- FDA Approved Viral Load Assays
  - To measure HIV-1 virus in plasma of infected individuals

- FDA Approved HIV Drug Resistance Assays
  - To measure drug resistance in individuals undergoing antiretroviral therapy
Companion Diagnostic - Definition

An in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product

Companion diagnostic device essential for:
- Identify patients who are most likely to benefit
- Identify patients likely to be at increased risk for serious adverse reactions
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation)
Regulation of Companion Diagnostic Device

FDA issued a draft guidance in July 2011
Draft Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices

- Device manufacturer will submit an application to FDA and reviewed under device authorities of FD&C Act
- Reviewed within the context of, or in conjunction with the therapeutic product
- Review carried out collaboratively with therapeutic review
- Risk based approach in reviewing the IVD
- Labeling review
Companion Diagnostics- CBER

“FDA will apply a risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices … the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket application (PMA) or, a 510(k)…”

“If an IVD diagnostic device is already legally marketed and the IVD diagnostic device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would consider the new use of the IVD diagnostic device with the novel therapeutic product a major change in the intended use of the device…”
Status of HIV Testing

- New FDA licensed / approved tests for blood screening, diagnosis, very rapid testing, and therapy monitoring
- Improved Prevention and Treatment: More people learning their HIV status
- Improvement in Blood Safety using NAT:
  - Window Period reduced to ~ 7 days, and
  - Residual risk of HIV transmission in transfused blood is 1 in ~ 3.1 million using NAT for individual donations
Estimated Residual Risk of Transmission of HBV, HCV, HIV by Blood Transfusion in the U.S.

HBV: *1 per 269,000 transfusions  
(Tests: HBsAg and anti-HBc)

HCV: *1 per 1,610,000 transfusions  
(Tests: Anti-HCV and MP HCV NAT)

HIV: *1 per 1,780,000 transfusions  
(Tests: Anti-HIV and MP HIV NAT)

*Busch, MP. Transfusion 2006; 46:1624-1640
Testing Blood for Transfusion for HBV

Consistent with current regulations and guidance documents all blood and components for transfusion in the U.S. are tested for:

- Hepatitis B surface antigen (HBsAg)
- Antibody to hepatitis B core antigen (anti-HBc)
The Committee supported routine blood screening blood by sensitive HBV NAT.

The Committee agreed that donations from persons with HBV "breakthrough" infections (vaccinees who are HBV NAT (+) / HBsAg (-) / anti-HBc (-)) are potentially infectious.
Status of HBV NAT

- FDA has discussed a Sensitivity Standard for screening of Whole Blood donations that is achievable by current HBV NAT assays and clearly shows utility.

- Issue of effectiveness of HBV NAT screening of Source Plasma was considered at BPAC in April, 2011.

- Final Guidance issued May, 2010 for reentry of donors deferred because of anti-HBc test results after 8 weeks using NAT and serology.
**West Nile Virus - Background**

**Summer 1999**: First outbreak of WNV in the US.

**September 2002**: Transmission of WNV by transplantation was confirmed, followed by the confirmation of transmission by transfusion (*MMWR 2002; 51(35):790*).

**July 2003**: Nationwide screening of blood donations for WNV RNA using NAT under IND on mini-pools (MP-NAT) of 6 or 16 donations, depending on the assay.
Background.....

**November 2003**: Evaluation of MP-NAT sensitivity to detect low viremia by retrospective studies using ID-NAT

- Identification of ID-NAT-positive and MP-NAT-negative units
- 6 confirmed cases of WNV transmission by transfusion of MP-NAT-negative units

**Summer 2004 and 2005**: Prospective testing by ID-NAT replaced MP-NAT in areas of high WNV activity during limited periods of time.
WNV Testing

• FDA licensed first WNV NAT for blood donor screening (Procleix® WNV Assay on eSAS) in December 2005.

• Final guidance Issued November 2009: Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion.

• Recommendation – Year round testing; Switching from MP-NAT to ID-NAT and back to MP-NAT.
WNV MP-NAT Unit/Donor Algorithm

1. Test each specimen in pool using ID-NAT
   - **Reactive**
     - Discard unit(s)
     - Defer donor for 120 days
     - Notify and counsel donor
     - Retrieve and quarantine in-date products from collections dating back 120 days
   - **Non-reactive**
     - If suitable, Unit Released

2. Reactive Master Pool with licensed MP-NAT for WNV
Babesiosis - Background

- Babesiosis, caused by infections of humans with intraerythrocytic protozoa of the genus *Babesia*, can be acquired through bites of infected ticks, or transfusion of blood from infected blood donors.
- *Babesia* transmission occurs mainly in NJ, NY, CT, RI, MA, WI, MN, but also in CA and WA.
- Transfusion-transmitted babesiosis (TTB) was first reported in 1979 and since then, more than 160 cases and 12 deaths have been reported.
- There is no FDA-approved test to screen blood donors for *Babesia*. 
Babesia Testing

• The majority of TTB cases are caused by asymptomatic donors who carry a low-grade infection but are not aware that they are infected

• Highly sensitive NAT can detect low grade infections in asymptomatic donors

• Recently donor testing by NAT and IFA tests has commenced under INDs at the Rhode Island Blood Center, RI to provide Babesia-tested blood to neonates and young children, and in selected blood donors in a few endemic and nonendemic states to collect data for test licensure.
## Nucleic Acid Tests Licensed for Donor Screening in USA

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Test</th>
<th>Analyte</th>
<th>Donation tested</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGI</td>
<td>UltraQual HIV-1 RT PCR</td>
<td>HIV-1 RNA</td>
<td>Source Plasma</td>
<td>9/18/2001</td>
</tr>
<tr>
<td>NGI</td>
<td>UltraQual HCV RT PCR</td>
<td>HCV RNA</td>
<td>Source Plasma</td>
<td>9/18/2001</td>
</tr>
<tr>
<td>Roche Molecular system</td>
<td>Cobas AmpliScreen HCV Test</td>
<td>HIV-1 RNA</td>
<td>Whole blood, Source Plasma, Cadaveric sample</td>
<td>12/3/2002</td>
</tr>
<tr>
<td>Roche Molecular system</td>
<td>Cobas AmpliScreen HIV-1 Test</td>
<td>HIV-1 RNA</td>
<td>Whole blood, Source Plasma, Cadaveric sample</td>
<td>12/20/2002</td>
</tr>
<tr>
<td>Roche Molecular system</td>
<td>Cobas AmpliScreen HBV Test</td>
<td>HBV DNA</td>
<td>Whole blood, Source Plasma, Cadaveric sample</td>
<td>4/21/2005</td>
</tr>
<tr>
<td>Roche Molecular system</td>
<td>Cobas TaqScreen Multiplex Test</td>
<td>HIV-1 RNA HCV</td>
<td>Whole blood, Source Plasma, Cadaveric sample</td>
<td>12/30/2008</td>
</tr>
<tr>
<td>Gen-Probe</td>
<td>Procleix West Nile Virus (WNV) Assay</td>
<td>WNV RNA</td>
<td>Whole blood Cadaveric sample</td>
<td>12/1/2005</td>
</tr>
<tr>
<td>Roche molecular System</td>
<td>COBAS TaqScreen West Nile Virus Test</td>
<td>WNV RNA</td>
<td>Whole blood, Cadaveric sample</td>
<td>8/27/2007</td>
</tr>
</tbody>
</table>
Summary

- In the U.S. all blood donations are tested for HIV-1, HCV, and WNV by MP-NAT in pools of up to 24.
- Source Plasma donations are also tested for HIV-1 and HCV by NAT.
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