FDA Update

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Bird’s Eye View

- Recent Events
- New Waivers
- Consensus Guidance - New Thoughts on Waiver Criteria
- Next Steps

Recent Events

- September 2003 - CLIAC Working Group Established (Gov't, Industry and Labs)
- February 2004 – Working Group Findings presented to CLIAC
- April 2004 – DHHS Delegates CLIA Categorization Authority to FDA

Recent Events (con't)

- As a result of Delegation – FDA assumes responsibility for developing waiver guidance based on Working Group's finding

- Draft guidance completion expected by end of year

New Waivers

- OraQuick HIV in fingerstick and venipuncture whole blood
- OraQuick HIV 1/2 in oral fluid, fingerstick and venipuncture whole blood
- Trinity Biotech HIV in venipuncture whole blood
- Cholestech LDX – AST in whole blood
- Thyrotec Inc. Thyrotest - Qualitative TSH in whole blood

Consensus Guidance

- High priority for FDA
- Based on CLIAC recommendations
- More flexible
- Scientifically more grounded -- AdvaMed based although devil in details

What's Not New

- **Simplicity (basically the same)**
  - Simple design - fully automated instrument, unitized, or self-contained test
  - Easy to run - no intervention during analysis
  - No specimen manipulation
- **Need for clear labeling**
  - 7th grade reading level
  - Use of quick reference instructions for use
  - Use of pictures and/or other methods for ensuring labeling will be understood

What's Not New

- **Need for flex studies, but**
  - Plan to link these more strongly to risk analysis
  - Plan to make these more scientifically based

What's A Little New

- **Moving from Lay-person (no training) to Intended user (person with limited training or hands-on experience in conducting laboratory testing). For example:**
  - Medical assistant
  - Nurse
  - Doctor

What's Gone

- **Postmarket surveillance requirements**
  - Decision made that due to complex distribution patterns this would be difficult to handle
  - FDA will explore more active and coordinated post-market surveillance systems to fill the gap

What's Gone

- **Requirements for reference methods/materials**
  - Recognition that only a small number exist
  - Appreciation that there are other methods for credentialing assays using principles in the ISO traceability document

What's Gone

- **Arbitrary QC requirements**
  - Instead of empiric QC requirements, waiver QC would be based on the risk analysis and data in use (ideally QC response under conditions of stress)

What's New

- **Traceability --** need for credible data
  - ISO document 17511 exists to allow for traceability of calibration for methods
  - Determining how to characterize uncertainty estimates is currently a bit uncertain
  - Addressing matrix effects will be challenging

What's New

- **Stronger risk analysis** and explanation for fail-safe or failure alert
  - ISO risk management document and IVD specific annex now exist in draft forms; FDA is working off stronger base for risk management

What's New for Accurate – Quantitative Study Design

- 3 sites w/ 3 or more intended users each
- 120 samples equally distributed - 360 total
- Consecutive patient samples
- Samples - span measuring range and collected over 30 days or more
- Each sample split for test device (WM) and for Comparator Method (CM)

Quantitative Statistics

- Descriptive Statistics for CM and WM
- Regression Analysis (95% CI for slope and intercept)
- Use regression equation to calculate the systematic bias at medically important point(s) (NCCLS EP-9)
- Total Analytical Errors using NCCLS-EP21and NCCLS C-28

Quantitative Performance Criteria

- Establish Allowable Total Error (ATE) for 99% of differences for WM
- Establish Limits for Erroneous Results (LER) for WM
- ATE and LER based on medical decision-making or on biological variations of measured analyte or Tonk's rule or other scientific approaches

Example of ATE and LER

- Clarke Error Grid Analysis used for whole blood glucose measurements
- Zone A is the ATE
- Zone D and E are the LER

What's New for Accurate – Qualitative Study Design

- 3 or more clinical sites and operators
- Use consecutive samples
  - 120 positive samples by CM
  - 120 negative samples by CM
  - Positive & negative samples equally distributed
- Split each sample - test one part WM and other part CM

What's New for Accurate – Qualitative Study Design Cont.

Near Cutoff Studies Being Developed

- Numbers
- Cutoff values studied
- Statistical techniques
- Endpoints

Plan Forward

- Internal draft and vetting
- External draft
- Creation of final guidance
- Creation of proposed rule
- Creation of final rule