



Managing Variability in Biospecimens: The Starting Line for IVD Development

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Medical Device Amendments of 1976

- General Controls
- Registration and listing
- Good manufacturing practices
- Reporting of adverse events



Assay Performance

Analytical

- Accuracy
- Precision
- Analytical specificity
- Analytical sensitivity

Clinical

- Clinical sensitivity
- Clinical specificity
- Predictive values



Labeling

- 809.10(b) – 15 requirements
- Intended use
- Performance
- Limitations
- **ADEQUATE INSTRUCTIONS FOR USE**



Quality of Studies– sensitive to multiple variables

- Plausible intended uses
- Quality of study design
- Correct data analysis
- Access to samples (prospective, cross-sectional, banked)
- **Quality of sample handling – how preanalytical variables are addressed**



Good News

- FDA is attentive to sampling issues
- Regulatory processes are transparent
- Regulatory processes try to reflect best practices



Bad News

- ❑ FDA is neither prescient nor omniscient
- ❑ Understands challenge to understanding specimen procurement and handling
- ❑ May not have any inside track on asking the right questions



Evidence Matters

- Peptide hormones
 - Original claims based on freezing
 - New studies suggest room temperature
 - New studies suggest rate of freezing can be determinative



Stored/archived samples

- ❑ Often used to generate analytical/clinical data
- ❑ Academic or commercial sources
- ❑ May be essential to avoid long term prospective studies



Stored/archived samples

Clear scientific evidence requirements

- Analyte stable over storage duration
- Adequate descriptive information
 - Population
 - Clinical diagnosis
 - Processing
- Sampling free from bias
 - Requires conscious effort
- Easier said than done



Stored/archived samples

- ❑ Clear legal requirements
- ❑ IRB
- ❑ Informed consent
- ❑ Exceptions (FDA does have guidance on use of leftover samples)



Leftover Samples

- “Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable”
 - Remnants of specimens collected for routine clinical care
 - Specimens from repositories
 - Specimens collected for unrelated research
 - NOT specimens collected specifically for current study

<http://www.fda.gov/cdrh/oivd/guidance/1588.pdf>



Leftover Samples

- ❑ Use without IC if donor not individually identifiable
- ❑ No result communicated to/associated with donor
- ❑ Preanalytical control may be precarious



Existing/emerging areas of concern

- Existing assays
 - Lability everywhere
 - Sample collection
 - Storage
 - Handling
 - Processing
 - External biological events (time of day, year)



Current review practices—existing assays

- Often sampling controls not well defined
- Often sampling controls not well described
- Often somewhat empiric



Current review practices—existing assays

- Worrisome for established assays in established matrices
- Worse for new assays in novel matrices (hair, saliva, tissues)
- Ad hoc formulation of controls for new assays
- Greater review focus on specimen information
 - Are we getting it right? What is existing evidence base?



Emerging issues

From Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis

“Specimen collection

You should evaluate all sample collection, transport, and storage options you recommend (e.g., **RNA preserving fixatives, frozen, fixed paraffin-embedded tumor tissue**). You should ensure that the test is validated using specimens that are handled in the same manner as will be recommended in the test label (e.g., collection, storage, shipment methods). You should validate that the **allowable elapsed time between tumor resection and preservation (e.g., by snap freezing, fixation or other methods)** results in uniformly acceptable specimens. You should specify the specimen transport conditions. You should validate that the **transport conditions** are adequate to ensure sample integrity, and to determine the limits of transport variability that are acceptable (e.g., **time in transit, quantity of coolant required**).

Your validation of appropriate storage conditions should include both the sample and the extracted RNA product. “



Ongoing Issues

- Optimal conditions and information for specimen difficult to obtain/assess for retrospectively collected specimens
- IVD sponsors have difficulty demanding prospective collection/handling parameters if no practice guidelines available and in use
 - Cost
 - Opportunity



Other Ongoing Issues

- In some cases, sufficient clinical information to determine whether samples are within the intended use population is not available
 - FDA requires studies in intended use population
 - Incomplete/absent clinical data for assessing how diagnosis was made can cripple/kill studies
 - Both unbiased selection and enrichment strategies impaired when clinical info not complete



Other Ongoing Issues

- Establishing what is truth (analytical or clinical)
- Paired samples to enable validation in multiple matrixes can be rare
 - Need paired samples to assess variability introduced by matrix/processing



Biomarker Studies/Combination Products

- In the context of drug development, studies to discover and validated biomarkers (predictive, prognostic, etc.) are likely to have similar issues but complicated by timing
 - Prospective specimen collection on phase 2/3 trials will benefit from standardized collection/storage/handling protocols
- If 3rd party diagnostic device is needed to direct therapy, measures to assure specimen comparability and quality will be needed.



FDA Mission

- Promote public health
- Protect public health
- Tension
- Good science