



Biospecimens & Companion Diagnostics: FDA Perspective

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The caHUB Biospecimen-Based Reference Sets for
Drug-Diagnostic Codevelopment Workshop
January 21, 2011



Companion diagnostic devices

In vitro diagnostic devices

- 1) that are necessary for the safe and effective use of the corresponding therapeutic products,
- 2) that are included in the instructions for use in the labeling of those products,
- 3) that are themselves labeled to guide use of a particular therapeutic, its generic equivalent, or class of therapeutics



Co-Development Occur When

The test is intended to identify patients

- for whom the drug is expected to be effective
- for whom the drug is expected to have minimal or no effect
- who would likely have serious adverse events
- who would likely receive greater benefit or have lower probability for adverse events on one drug than another.

The test is intended to be used to

- monitor response to drug therapy
- select doses of the drug most likely to be effective and/or safe for the patient



Intended use

- “Intended Use” of the device is a key factor in the evaluation of a pre-market submission
- Specific claims made in the Intended use must be supported by appropriate performance characteristics data



Intended Use/Indications for Use

- Target condition
 - Disease, condition
- Purpose of test
 - Diagnostic, predictive, etc
- Analyte(s) measured
 - RNA, DNA, protein, metabolite, etc
- Target population
 - Who will be tested

- Specimen
 - Primary tumor, FNA, bone marrow aspirate, biopsy
- Matrix
 - Whole blood, FFPE, serum, etc
- Result type
 - qualitative, quantitative, etc
- Setting
 - POC, clinical lab



Clinical Validation of a companion diagnostic device

- Ideally, the test should be clinically validated in Phase III drug trial, so the clinical performance is supported by the Phase III clinical trial data
- Training set should be distinct from validation sample set
- Test should be analytically validated before the clinical validation



Challenges

Test used in drug trial is not the version intended for marketing:

Sponsors should be prepared with a bridging study.

Need plan for sample acquisition, storage, and access for retest analysis (SAVE both screen negative and screen positive)

Concordance at cut-off is critical



Challenges

Missing samples

- Need to control for bias due to lost samples
- Need both screen negative and screen positive
- Need well annotated records (e.g., demographics, previous treatments and other factors that affect the test such as tumor size, % tumor content, sample quality).



The use of retrospective samples

The use of retrospective samples is conditional on several key factors including whether :

- (1) the storage conditions for the specimens do not impact the assay,
- (2) specimens are representative of the intended use of the device, need well annotated records
- (3) specimens are consecutive cases meeting a set of inclusion/exclusion criteria
- (4) the performance assessed is comparable to that expected with a prospective study.



Stored Specimens

- Annotated?
 - Demographics, diagnosis, treatment history, etc.
- Match IU population?
 - Geography, age, disease stage, etc?
- Consented?
- Bias?
 - Collection setting, specimen age, size, etc.
- Storage history?



Matrices

- For validation
 - Must account for all claimed matrices
 - How uniform is “matrix”?
 - FFPE processing
 - » Fixative
 - » Quality
 - » Duration
 - How long is analyte stable in matrix?
 - What storage conditions are required?
 - Is purification, concentration required?
 - Does matrix interfere with measurement?



FDA Issues

- Test is developed and validated in a way that supports clinical diagnostic use in intended population (intended use)
- Studies to validate test are controlled—analytically, and for patient safety
 - *Informed consent*, IRB oversight, investigational use
- Test instructions for use actually correspond to reality



Biospecimen Benefits

- Better discovery
- Better tests
- Patient benefit
- **GOOD SCIENCE**



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Back-up slides



Biospecimen Quality Matters

- Test development
 - Discovery
 - Validation
 - Instructions for use
- Test use
 - Adequate collection, preparation (pt, specimen, etc)
 - Correct measurement
 - Correct interpretation



Specimens

- For validation
 - Must be able to show that test works on specimen type (patient) to be used
 - Access to appropriate specimen types, e.g. biopsy
 - Evidence that specimen source (patient) meets intended use population, e.g., age, sex, disease state
 - Specimens handled/stored in controlled manner?
 - Often need treatment history, e.g. prior therapy



Testing

- Instructions for use
 - List of variables to be controlled
 - Patient preparation and concurrent exposures
 - Procedures needed prior to testing, e.g., LCM, macro, etc.
 - Control materials



Societal Costs

- Failed discovery
 - Inadequate
 - Specification of IU population
 - Specification of specimen parameters
 - Control materials
 - *Availability of useful specimens*



Patient Costs

- Inconsistent test results
 - No/poor mechanisms to control/manage specimen collection variables
 - Lack of recognition that variables matter
 - Lack of standards (material or method) to trace collection/handling/storage history



Possibilities

- In an ideal discovery and product development world
 - Well-curated specimen collections with:
 - Complete demographic cross-section
 - Complete handling/storage history from moment of collection
 - Complete patient history
 - Matched specimens from same patients
 - Broad informed consent