



The Importance of Biospecimen Quality in FDA Submissions

Abraham Tzou

Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and
Safety
FDA/CDRH

Biospecimen Research Network Symposium
March 29, 2011

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

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?

Stored Specimens

- Annotated?
 - Demographics, diagnosis, treatment history, etc.
- Match Intended Use population?
 - Geography, age, disease stage, etc?
- Consented?
- Bias?
 - Collection setting, specimen age, size, etc.
- Storage history?
- Does storage reflect future use?

Testing

- Instructions for use
 - List of variables to be controlled
 - Patient preparation and concurrent exposures
 - Procedures needed prior to testing
 - Control materials

Societal Costs

- Failed development
 - Inadequate
 - Specification of Intended Use 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

FDA Issues

- Test demonstrates performance 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



Key Elements in In Vitro Diagnostic (IVD) Submissions

- Intended Use (IU)
What is device supposed to do?

- Indications for Use (IFU)
When should it be used?

- Both analytical and clinical data are supporting evidence for Intended Use and Indication For Use

Intended Use Statement (how/by whom device is used)

- ❑ What is the device measuring, identifying or detecting? (analyte, organism, ..)
- ❑ Specimen types, sources (whole blood, serum,..)
- ❑ Conditions for use (hospital lab, home use,..)
- ❑ What type of data output?
(quantitative, qualitative, semi-quantitative)

Indication for Use Statement (for what/on whom device is used)

Target condition

- a particular disease, a disease stage, health status, or any other identifiable condition of event within a patient

Target population (intended use population)

- those subjects for whom the test is intended to be used

Medical Testing Contexts

- as, for screening, diagnosis, monitoring, prognosis and so on.

Examples of IVD Medical Testing Contexts

- ❑ **Diagnosis** (target condition is present or not during the time of testing)
- ❑ **Screening** (maybe in a general population [asymptomatic subjects at average risk] or a subpopulation [subjects at high risk])
- ❑ **Risk assessment** (assessment of predisposition to disease in future)
- ❑ **Prognosis** (stratifying already diagnosed cancer patients into poor or good prognosis)
- ❑ **Monitoring** (is therapy working for a patient?)
- ❑ **Companion Diagnostics/Co-development paradigm**
(Therapeutic response prediction)

* This is not a comprehensive list

Intended Use/Indication For Use drives:

- Study design
- Kinds of patients (Asymptomatic,..)
- Clinical sites (e.g. doctor's office, ER, hospital)
- Sample size justification

.....

N subjects in the clinical study
(N subjects from target population)

Every subject



Test under investigation:

Positive,
Negative

Clinical Reference Standard (Gold Standard):

D+ = Target condition present,
D- = Target condition absent

We considered an ideal scenario when N randomly selected subjects are from the intended use population and each subject has result of the test and verification of disease ($D+$, $D-$).

Potential Biases

- 1) Selection bias (when the study population does not represent the IU population) – spectrum bias
- 2) Verification bias

Banked (retrospective) samples (potential selection biases)

How representative are banked samples (inclusion/exclusion criteria)

Only leftovers from big tumors (sample volumes)?

Storage does not impact analyte of interest

Provide unbiased estimates of performance

Spectrum Bias

Example

Diseased subjects in the Intended Use population =
50% of Stage II and 50% of Stage I

Test ABC has sensitivity for Stage II = 90%; Stage I = 50%

Sensitivity of test ABC in the IU population =
 $0.5 * 90\% + 0.5 * 50\% = 70\%$

Retrospective samples in the clinical study
80% of Stage II and 20% of Stage I:

Sensitivity in the clinical study = $0.8 * 90\% + 0.2 * 50\% = 84\%$

Sensitivity is biased (overestimated)

Verification Bias

Example

Clinical study with 100 subjects: each subject has verification of disease and test result

		Gold Standard		Total
		D+	D-	
Test	Pos	20	5	25
	Neg	30	45	75
Total		50	50	100

$$Se = 40\% (20/50)$$

$$Sp = 90\% (45/50)$$

Example (cont.)

Subjects were referred to the GS based on the “Current clinical practice”.

In the study, all 25 subjects with pos. test results -> GS; only 1/3 of 75 subjects with neg. test results -> GS.

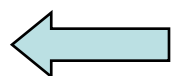
Analysis of the data with verified disease status

		Gold Standard		Total
		D+	D-	
Test	Pos	20	5	25
	Neg	10	15	25
Total		30	20	50

Se = 67% (20/30)

Sensitivity is biased (overestimated)

Sp = 75% (15/20)



Specificity is biased (underestimated)

Verification Bias

occurs when a non-random group of subjects in the clinical study selectively receive clinical reference standard.

Prostate cancer

T_{New} – new biomarker as an aid to make a decision who needs a prostate biopsy

Complex pattern describes how subjects are referred to prostate biopsy (current practice uses age, race, digital rectal exam, PSA, family history...)

How to evaluate T_{New} in unbiased way?

Very challenging problem!

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 and follow-up
 - Matched specimens from same patients
 - Longitudinal specimens
 - Broad informed consent



Biospecimen Benefits

- Better discovery
 - Better tests
 - Patient benefit
 - Good Science
-
- Address variability and bias



Thank You

abraham.tzou@fda.hhs.gov