



U.S. Food and Drug Administration

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Issues in Clinical Trial Design for Diagnostics and Combination Products

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■ ■ ■ Presentation Outline

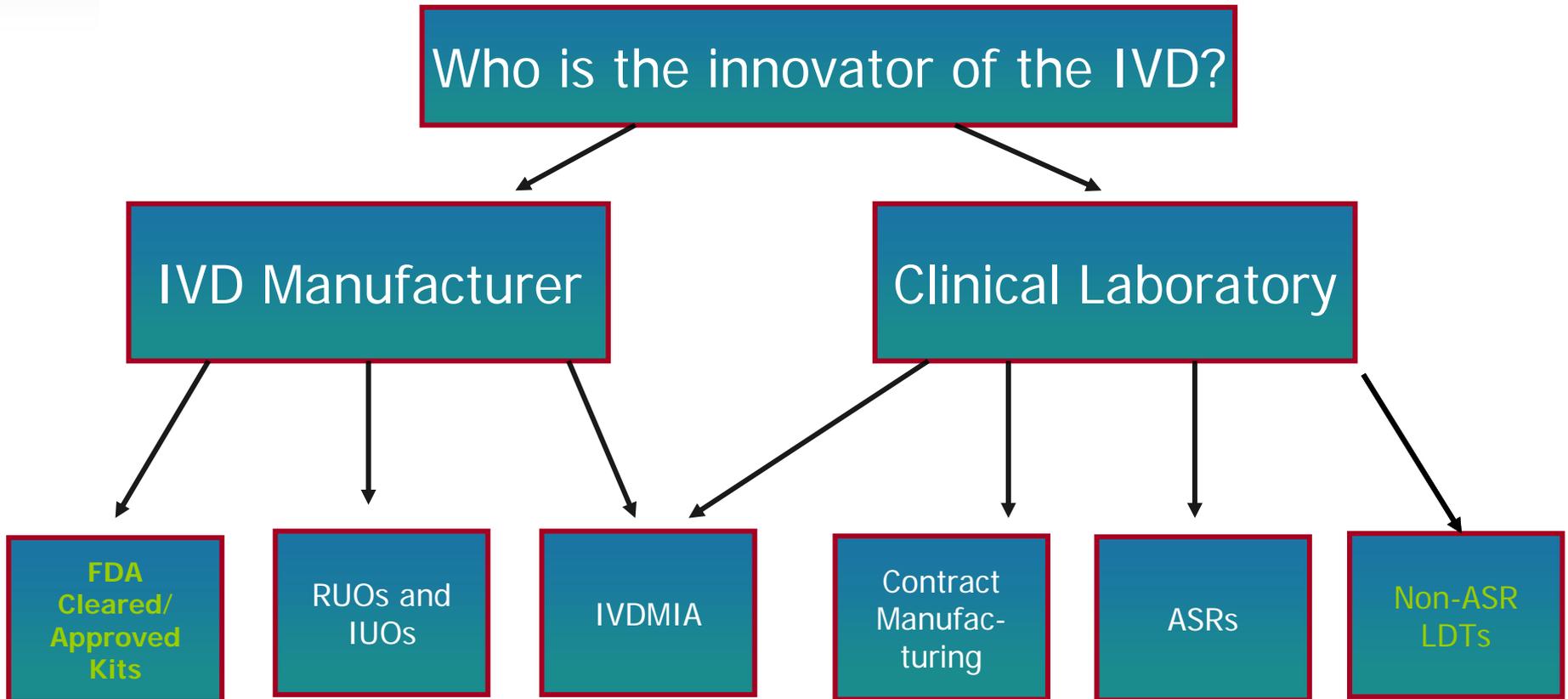
- Overview of Regulation of In Vitro Diagnostic Devices (IVDs)
- Scope of Data to Support Approval/Clearance of an IVD Device
- Companion Diagnostics
Co- development: Benefits and Challenges
- Useful Tools



Definition of an In Vitro Diagnostic Device

“Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. ... for use in the collection, preparation, and examination of specimens from the human body.”
[21 CFR 809.3]

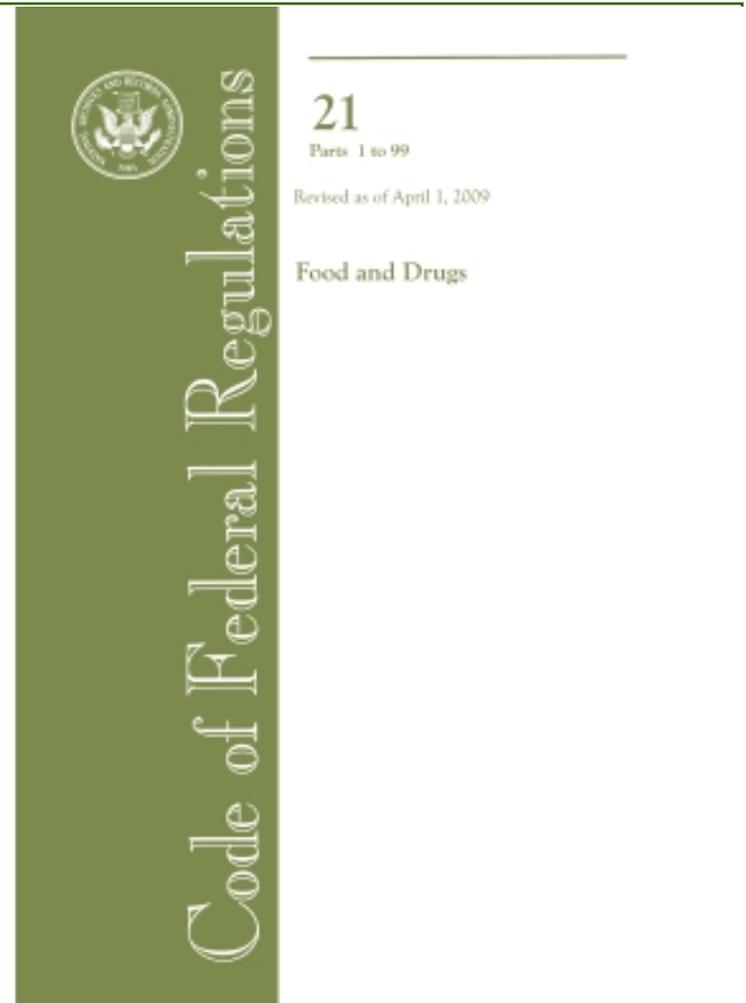
Sources of IVD Devices





Regulatory Authority

- Federal Food, Drug and Cosmetic Act
 - Established regulatory controls for Medical Devices (May 28, 1976)
- Code of Federal Regulations, Title 21, Part 800





Human Subject Regulations

Definition of a “Human Subject”

- Human who participates in research either as a recipient of the test article or as a control. A healthy human or a patient
- Subject is an individual on whom or on *whose specimen* an investigational device is used



Human Subject Protection Regulations

- **21 CFR Part 50:** Informed consent and limited emergency exceptions
 - **21 CFR Part 56:** IRB review
 - **21CFR 812:** Disqualification of an Investigator (812.119)
- Apply to all FDA clinical investigations

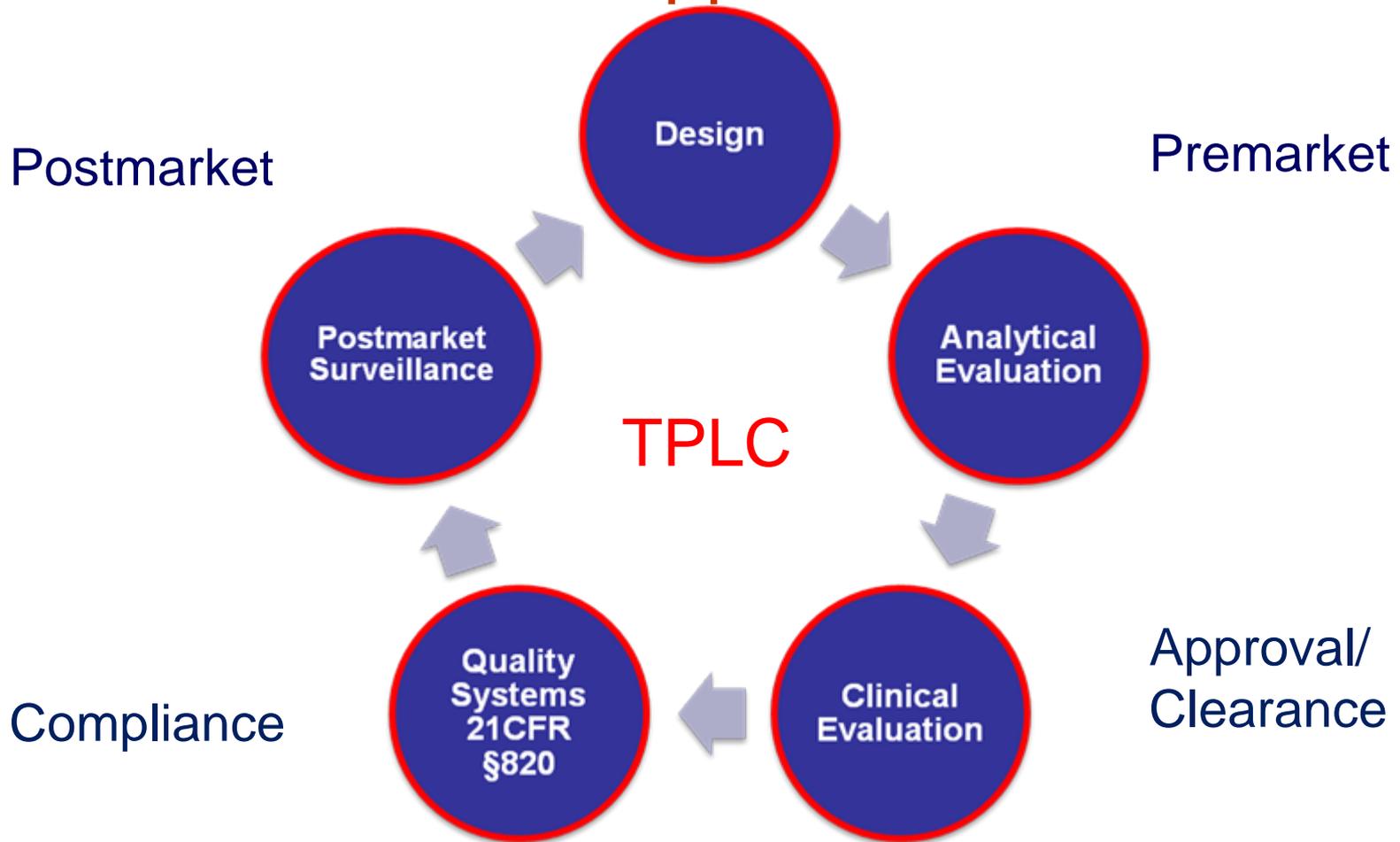


Guidance for Sponsors, IRBs, Clinical Investigators and FDA Staff

“Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable”
(4/25/2006)

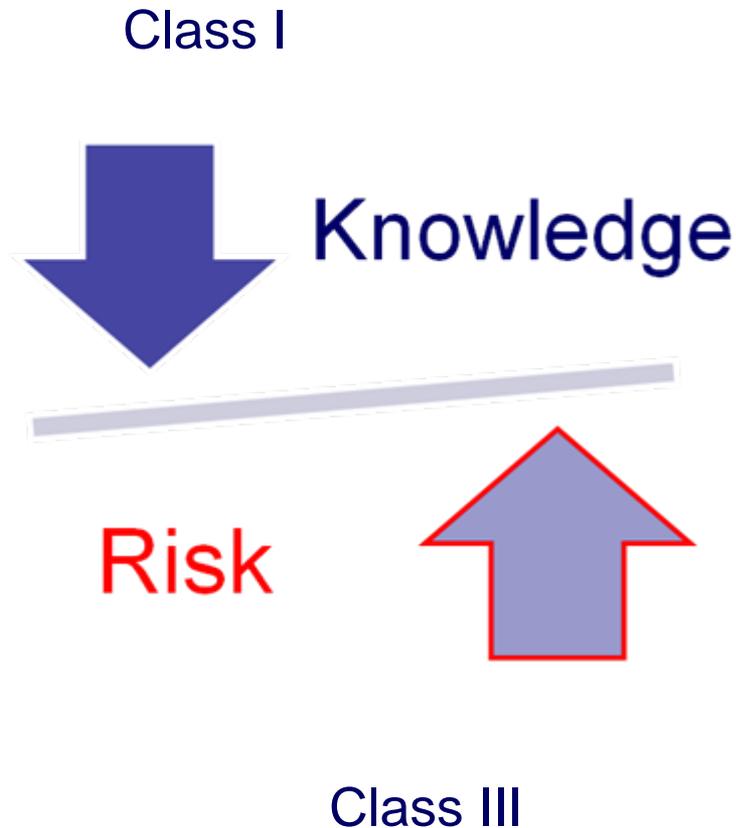
<http://www.fda.gov/cdrh/oivd/guidance/1588.html>

Total Product Life Cycle Regulatory Approach



<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTPLC/tplc.cfm>

Pre-market Risk Based Regulation



Knowledge Mitigates Risk

- Class I - Low likelihood of harm
Register & list
General Controls.510(k)
- Class II - Moderate likelihood of harm
or risk can be mitigated
Special Controls. 510(k)
- Class III - High or unknown
likelihood of harm
Significant Risk
Pre-market Approval



Basis of Pre-Market Device Review: Safety and Effectiveness

- **Safety**

- *Are there reasonable assurances, based on **valid scientific evidence** that probable benefits to health from use of the device outweigh any probable risks?*
[860.7(d)(1)]

- **Effectiveness**

- *Is there reasonable assurance based on **valid scientific evidence** that the use of the device in the target population will provide clinically significant results?* [860.7(e)(1)]



Intended Use of the IVD

The “**Intended Use**” is the driving force of the scientific review

- Understanding the disease(s)/condition(s). Integration of patient clinical management and public health (surveillance)
 - **Who** will be tested, where and when: outpatients, inpatients, pediatrics, adults, acutely ill, etc.
 - **What** are the appropriate specimens: timing, handling
 - **How** result(s) may be used: patient management



Scientific Review : Device Performance

- **Analytical** Performance Characteristics
Reliability and accuracy of analyte measurements
- **Clinical** Performance Characteristics
Clinical sensitivity and specificity
Positive and negative predictive values
- **Labeling**
Intended use, device design, directions for use,
warnings/limitations, result interpretation, performance



Demonstrating Evidence for Safety: Analytical Studies

- Likelihood of false positives
 - Cross-reactivity and other interferences
 - Carryover and contamination
- Likelihood of false negatives
 - Limits of detection
 - Matrix effects
 - Interference



Demonstrating Evidence for Effectiveness: Clinical Studies

- Well-controlled clinical evaluations:
 - Clinical plan and protocol
 - Defined objective(s) and methods
- A test device with standardized design and performance
- Other evidence: case histories, literature, reproducibility etc.



FDA Guidance Relevant to In Vitro Diagnostic Device Clinical Trials

- “In Vitro Diagnostic (IVD) Device Studies- Frequently Asked Questions”

Published 10/25/07

<http://www.fda.gov/cdrh/oivd/guidance/1536.pdf>



Companion Diagnostic Policy Emerges..

- Healthcare practitioners rely on information from companion diagnostic devices to help make critical treatment decisions
- Companion diagnostics
 - Provide benefit in optimizing treatment
 - Bring risk if test result is incorrect



What is a Companion Diagnostic?

- A companion diagnostic device is a medical device that identifies/determines a condition of use for a therapeutic product and is important to ensure the safe and effective use of that product.
 - *If the safe and effective use of the therapeutic product requires a particular test result, that test is a companion diagnostic*

■ ■ ■ Draft Guidance Published

- “*Draft Guidance for Industry and FDA Staff; In Vitro Companion Diagnostic Devices*” published July 14, 2011
 - Docket FDA-2011-D-0215
 - Comment period extended to October 12, 2011



Regulatory Concept: Premarket Review

- Premarket review and clearance or approval of the companion diagnostic will typically be required prior to or contemporaneously with approval of the therapeutic product
 - Assurance that the diagnostic has been appropriately validated for its intended use
 - Risk-based regulation applies



Regulatory Concept: Co-approval

- Companion Dx and therapeutic product depend on each other
- Co-approval required*
- Failure/lack of test approval = no therapeutic product approval

* Exceptions will exist



What Types of Tests Could Be Companion Dx?

- Identify patients likely to respond or not respond to a particular medical product
 - *Predictive test* that can select either a population that is likely to respond, or a population that is not likely to respond
 - Generally validated in Ph 3 trials, although could be a post-approval addition, e.g., KRAS



What Types of Tests Could Be Companion Dx? (2)

- *Identify* subgroups of the larger population with *poor prognosis* who are likely to benefit from a particular therapeutic product
 - Test selects those who might benefit from treatment with a therapeutic product due simply to otherwise poor prognosis



What Types of Tests Could Be Companion Dx? (3)

- *Identify* patients likely to be at **increased risk for serious adverse reactions** as a result of treatment with a particular therapeutic product (*predictive*)
 - Could be a test to show patient likely to, or unlikely to suffer SAR
 - Validation design can be tricky
 - Consideration of whether other therapies are available, seriousness of disease to be treated



What Types of Tests Could Be Companion Dx? (4)

- *Monitor* response to treatment for the purpose of *adjusting treatment* (schedule, dose, etc) to achieve improved safety or efficacy
 - Specific test performance needed, specific test values critical
 - Not generally accepted biomarkers for status



What Types of Tests Could Be Companion Dx? (5)

- *Individualize the dose* of particular therapeutic product
 - Predicts safe/effective dose based on specific test result



What Types of Tests Could Be Companion Dx? (6)

- *Use as integral part of therapeutic clinical trials* conducted to support market approval of a therapeutic product
 - *selection of trial participants*
 - primary trial analysis performed using diagnostic device data to demonstrate therapeutic performance
 - *If test was used in any way to define trial success, it will need to be available to select the same population when therapeutic is approved*



Examples

FDA cleared / approved device in reference to the drug
FDA drug package insert sites the relevant test

Efficacy Test	Safety Test	Drug
HER-2/neu IHC, FISH & CISH		Trastuzumab (Herceptin)
c-kit IHC		Imatinib mesylate (Gleevec)
EGFR IHC		Cetuximab, Panitumumab
BCR-ABL or t(9:22)		Imatinib mesylate (Gleevec)
EGFR mutations		Gefitinib, Erlotinib
	UGT1A1 mutations	Irinotecan
	TPMT	6MP & Azathioprine
	CYP450 (2D6) mutations	5-HT3R antagonist, codeine derivative
	CYP2C9 & VKORC1	Warfarin





Co-development Questions Pertaining to both Diagnostic and Drug

- **Diagnostic Use**

- Does the test make a difference?
- What if the assay parameters (or the assay itself) changes during or after development?

- **Drug Development Program**

- Acceptable sequential or single adaptive trial designs?
- Evidentiary standards
- Generalizability, multiplicity, and other problems

■ ■ ■ Co-development Benefits

- Evaluate drug and device in one trial
- For pharmaceutical companies
 - potential for optimum patient population and smaller future trials
 - improved drug effect if marker effective
- For diagnostic companies:
 - new type of diagnostic claim
 - well characterized subjects
 - extensive follow-up

Pathway from Pre-Clinical to Launch - Ideal Time Lines

Drug Developmental Pathway

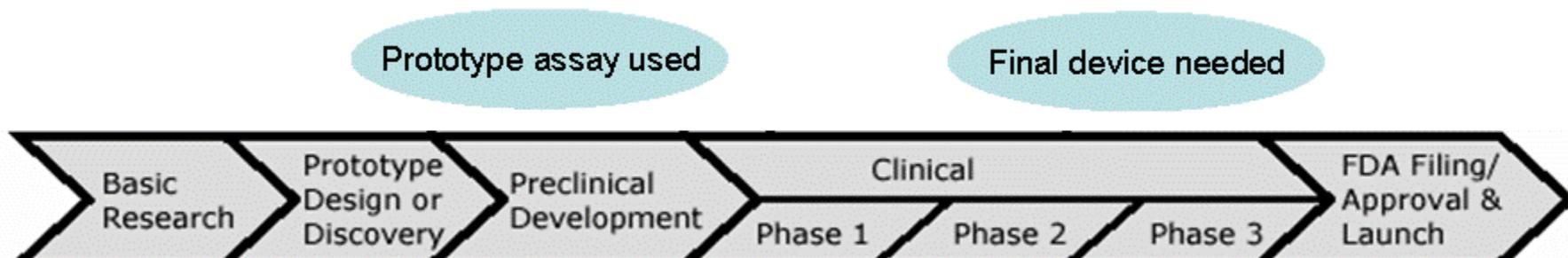


Device Developmental Pathway





Challenges of Co-development (1)



- May not be adequate data early on to determine the best biomarker to measure; whether test needed
- Appropriate statistics (may allow for e.g., adaptive trial design if drug not effective in the general population)
- Test used in drug trials not the marketed version (platform change)
- Appropriate storage of clinical trial samples; IRB, IC

■ ■ ■ Challenges of Co-development (2)

- Test analytical performance not validated prior to use in clinical trial
- Multiple tests (with different performance?) used to enroll subjects in clinical trial
- Bridging studies from CTA to companion Dx need high sample ascertainment ($\geq 90\%$ recommended)
- No way to determine test performance if only marker + samples available
 - Results in selection, but not predictive, claim

■ ■ ■ Challenges of Co-development (3)

Enrolment Issues:

- If test is part of inclusion/exclusion criteria for therapeutic trial
 - Use a central site to do ALL testing (not confirmation of local test)
 - or:
 - Use SAME test (same demonstrated performance characteristics) at ALL sites
- AND:
- Assure any test used has adequately validated measurement characteristics (analytical validation)

■ ■ ■ Analytical Validation

- Use a test for patient selection/stratification that has been as completely analytically validated as possible, with acceptable performance characteristics
- For tests that detect multiple possible genetic changes, e.g., multiple mutations within a gene, should be analytically validated for each change to be detected.
- When performing analytical validation, consideration should be made of the ultimate specimen source to be used once drug is on the market, i.e., FFPE tissue, blood, CSF

■ ■ ■ Testing Protocol/Samples

- Neither the test nor the testing protocol should be altered once the pivotal trial is begun
- Sponsors should save samples from *all* patients enrolled in the trial. When only test-positive patients are enrolled:
 - do not prescreen for eligibility with a different test
 - save samples from patient who are test-negative and are thus not enrolled in the trial
- If a change in specimen type is anticipated for future testing, obtain paired samples on initial testing
- For any samples that have been stored prior to testing, perform validations to assure that analyte is stable under storage conditions

■■■ Policy and Guidance

- Schedule pre-IDE meetings with CDRH as soon as a test has been identified. Discuss design of clinical studies etc. Helpful to have both diagnostic and pharmaceutical reps.
- Alert FDA center that therapy application includes a diagnostic device
- Companion diagnostics require compliance with FDA medical device regulations, even if laboratory developed
- A test approval/clearance will be needed prior to drug approval in most cases
- Final intended use of the test will often depend on outcome of therapeutic clinical trial

■ ■ ■ Clinical Validation of Companion Dx

- Companion Dx (or its prototype or CTA) used within pivotal therapeutic trial
 - No systematic difference whether normal or accelerated approval of therapeutic
- Analysis of diagnostic device performance related to therapeutic trial outcome
 - Therapeutic trial fails = diagnostic not informative
 - Therapeutic trial succeeds = diagnostic (generally) informative
 - Diagnostic label will reflect use in pivotal trial
 - Generally, no additional clinical validation of diagnostic needed
 - For predictive claims, therapeutic trial should be powered to detect differences in response by diagnostically defined strata.

■■■ Relabeling of a Therapeutic

- When new evidence becomes available to address a serious safety issue for an approved therapy
 - Relabeling of the therapy to include a test may be appropriate
 - Required test—test must usually be approved and available at time of relabeling
 - Recommended test—test ideally to be approved, but label change will not be delayed for approval

■ ■ ■ Conclusions- Co-development

- Drug-device trial allows for evaluation of broader range of claims
- Many complex issues in designing studies
- Use of unapproved /cleared IVD s or off label use of unapproved/cleared tests
- Use CDRH pre-IDE process and CDER pre-IND process when planning study design and execution
- More research and collaboration between diag./drug companies is vital



Tools: Standards for Evaluating Diagnostics

- Medical Devices Standards Database
 - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm>
- Clinical Laboratory Standards Institute (CLSI)
 - develop global consensus standards and guidelines for healthcare testing (industry, government, professional)
 - www.clsi.org
 - Evaluation Protocols (EP) for study design/analysis
- ISO (International Standards Organization)
 - has standards for estimating bias and imprecision of test methods



Select CLSI Documents

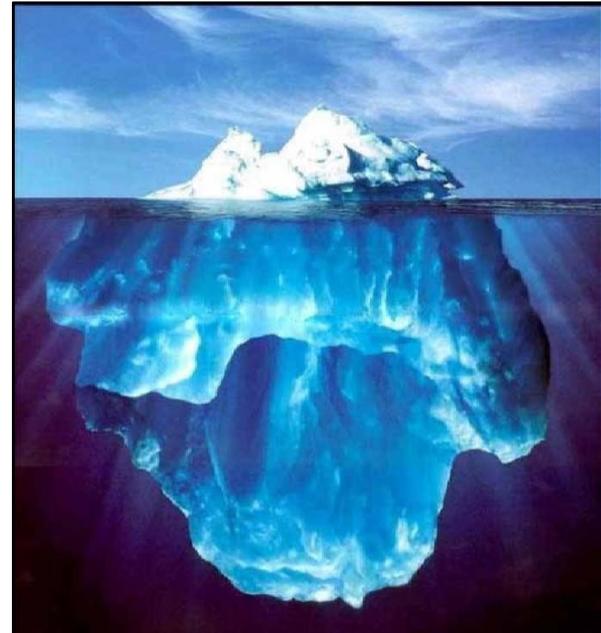
- C28-A3. Reference Intervals
- EP5-A2. Evaluation of Precision Performance of Quantitative Measurement Methods
- EP6-A. Evaluation of the Linearity of Quantitative Measurement Procedures
- EP9-A2. Method Comparison and Bias Estimation Using Patient Samples;
- EP12-A2. User Protocol for Evaluation of Qualitative Test Performance
- EP17-A. Limits of Detection and Limits of Quantitation
- EP21-A. Total Analytical Error
- GP10-A. Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots;
- MM17-A. Multiplex Nucleic Acid Assays



Information:CDRH Homepage-Diagnostics

www.fda.gov/cdrh

- **Device Classification Database**
- **Device Advice**
 - <http://www.fda.gov/cdrh/devadvice>
- **Register for “What’s New”**
- **Guidance Documents**
- **IDE Information**
 - <http://www.fda.gov/cdrh/devadvice/ide/index.shtml>
- **Much more...**





Summary of Presentation

- Covered Overview of Regulation of In Vitro Diagnostic Devices (IVD)
- Covered Scope of Data to Support Approval/Clearance of an IVD Device
- Discussed the Benefits and Challenges of Co-development for Companion Diagnostics
- Useful Tools

