Co-Development of an In Vitro Companion Diagnostic Device with a Therapeutic Product

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Companion Diagnostic Guidance

- Developed by CDRH, CDER, and CBER

- **"Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product"**
  - Draft guidance published on July 15, 2016
  - Public comments submitted to the docket considered in finalization of the guidance
  - Describes best-practices in co-development
- **"In Vitro Companion Diagnostic Devices"**
  - Defined companion diagnostic (abbreviated as CoDx or CDx)
  - Described regulatory requirements (e.g., co-approval, labeling)
  - Finalized August 2014

Content of the Co-development Guidance

- General
- Regulation of Investigational IVDs and Therapeutic Products
- IVD Development – Planning Ahead
- Therapeutic Product Clinical Trial Design Considerations
- IVD Development in Later Stages Development
- Coordinating Review
- Labeling Considerations
- Postmarket Considerations

Focus of this presentation:

- Regulation of Investigational IVDs – Answers to Common Questions
- IVD Development – Planning Ahead Tips
- Missing samples
- Additional tips for PMAs

While this presentation includes a discussion of regulatory strategies and processes, they might not apply in all scenarios. Every situation is considered on a case-by-case basis.

Companion Diagnostic - General

- Definition is focused: essential for the safe and effective use of a corresponding therapeutic product;
- "Essential" determined by CDER/CBER
- "Follow-on" devices intended to be used as CDx should plan to validate
- FDA has experience with several kinds of applications: IVD manufacturers, LDTs, HDEs, Follow-ons
- Can review the "Summary of Safety and Effectiveness" at "List of Cleared or Approved Companion Diagnostic Devices"
  http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm?source=govdelivery

What is (generally) not a CDx?

- Tests that are medically established and collectively recognized as necessary for the diagnostic work-up of a patient:
  - Hereditary tests that are part of the diagnosis (e.g., Kaleydeco, Exondys 51)
  - Exceptions: when there may be multiple methods that will yield discordant results (e.g., diagnostic sub-classification, prognostic assays)
- Tests used to assess benefit-risk within an approved population (i.e., complementary diagnostics)
- Basic laboratory tests that are part of the patient record (e.g., creatinine)
- Tests used as surrogate endpoints for drug safety and efficacy

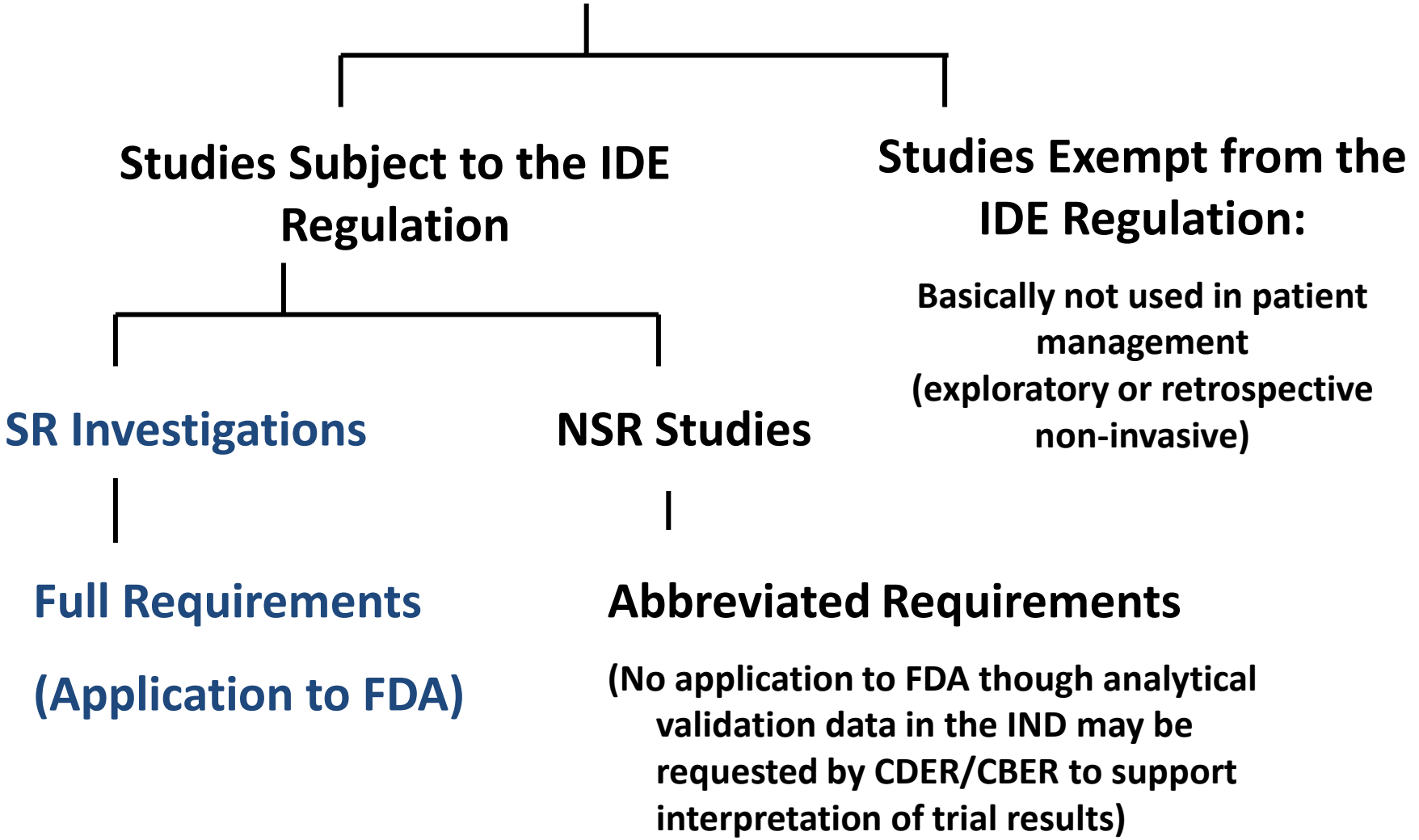
Investigational Devices

- Both have own regulatory requirements
  - Therapeutic Product: Investigational New Drug, 21 CFR 312
  - IVD: Investigational Device Exemption (IDE) Regulation, 21 CFR 812

- Compliance with one doesn't fulfill compliance with the other

- An IVD is investigational if used for a purpose that has not already received marketing authorization for that specific intended use /indication

Investigational Device Exemptions (part 812)



Do I need an IDE?

- Need for an IDE is based whether or not you have an exempt investigational device
- Need for an *IDE application* to FDA is based on risks to patients
- Significant risk device requires an approved IDE application,
- Non-significant risk device is by default considered to have an approved IDE.
- Irrespective of phase or number of patients
- Testing sites should comply with IDE requirements when in the US *or* testing US patients (i.e., does not apply for foreign testing of foreign patients)

How do I determine if I have an SR investigational device

- IRB can decide risk
- To ask FDA: use the Study Risk Determination pre-submission process through CDRH (30 day internal review)
- Include a cover letter and copy of clinical trial
- Can offer rationale to support NSR determination
- Determination made for the protocol/version
- Can ask whether an IDE is needed in the IND, but you will not receive a formal determination.

What are the criteria for Significant Risk Devices?

21CFR 812.3(m)Significant risk device means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

- However, in the case of investigational devices used in clinical trials with an approved IND, the scope of the SR determination is refined…

SR Determination Process for Investigational Devices used in Clinical Trials Conducted under an Approved IND

Given that patients have agreed to the risks of the investigational therapeutic and are monitored for safety in the IND- what is the additional risk posed to the patient due to the device use?

1. Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?
    - Therapeutic options do not have to be FDA approved, but might be recognized in guidelines
    - Largely concerned with false positives (enrollment leads away from Rx options) and not false negatives (determined ineligible for a trial because benefit has not been proven)
    - Does not consider patient “unwillingness” on par with no treatment options

SR Determination Process for Investigational Devices used in Clinical Trials Conducted under an Approved IND

…continued

2. Will use of the investigational test expose the patient to AEs worse than the SOC;

3. Is there information that outcome with therapeutic is worse in a subset of patients defined by the test;

4. Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?

Examples

- NSR
  - Patients with relapsed or refractory disease who have exhausted their treatment options
  - Trial enrolls all-comers but stratifies based on biomarker;
  - Trial enrolls marker subset but the treatment is in combination with the SOC;
  - Use of archived tumor tissue only
- Portions of a trial may be SR e.g., Biomarker –based expansion cohorts, study arms in umbrella trials, subpopulations in basket trials

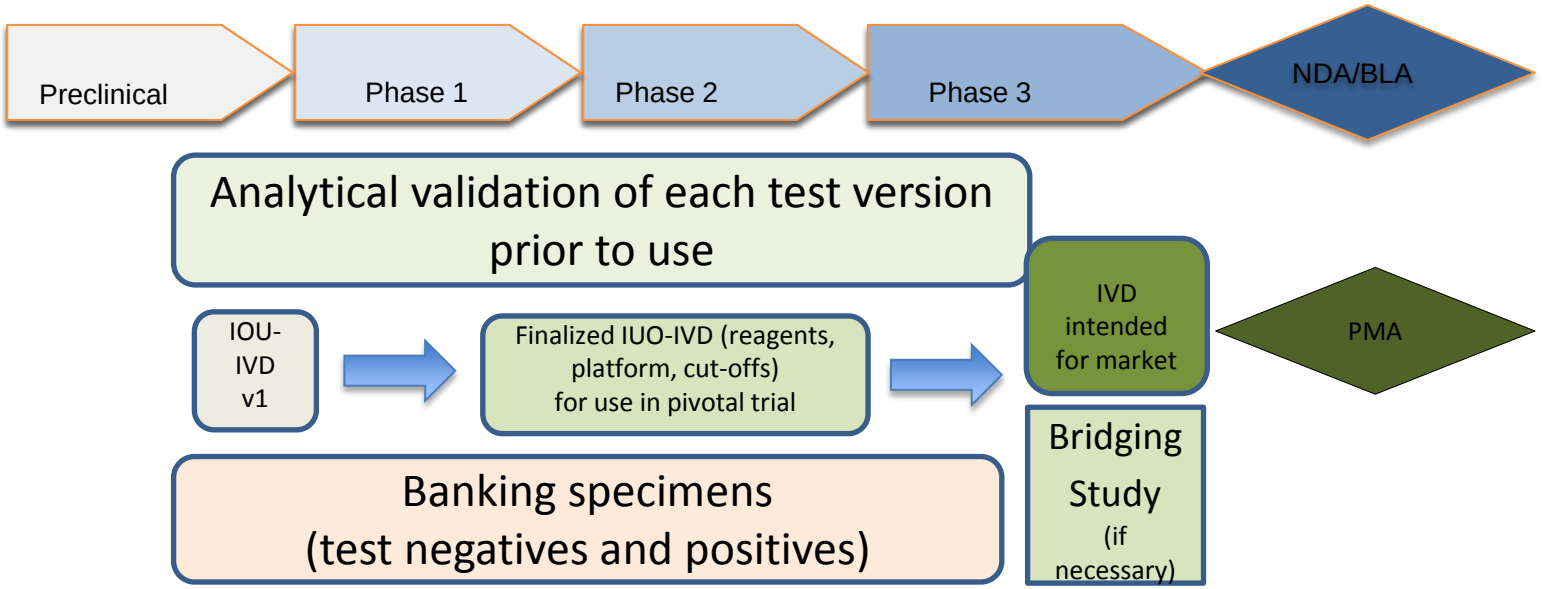
Mutation testing patient tumor specimens is part of a patient work-up, why do I need a CDx?

- Genetic testing of tumor specimens is generally done to optimize selection of therapeutics.
- Other indications for this testing (e.g., prognostic) may employ different cut-offs
- Need to demonstrate analytical validity of test performance for CDx use and establish cut-offs for the Rx selection
- Tests used to identify responders for investigational therapeutic indications is an investigational use until proven in a clinical trial.

Submitting an IDE application

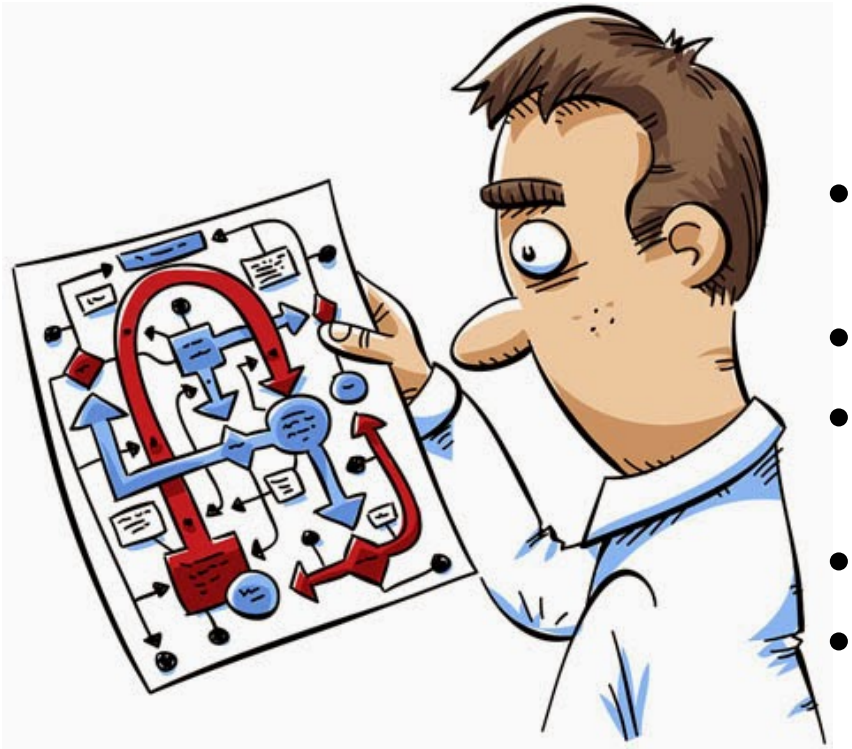
- IDE studies not expected to be the same as PMA studies
- Reviewed for safety, not effectiveness
- Analytical studies to demonstrate that the test is sufficiently reliable, particularly around the clinical decision point(s).
- Can submit supplements to approved IDE for new trials (assuming device is the same)
- Considerations given to phase 1/feasibility studies (e.g., cell lines/plasmids)
- Administrative elements
- Informed Consent should indicate the investigational device
- What to do if I have multiple LDTs, does each one need to submit an IDE application? Recommend a central testing lab to confirm results and submit the IDE application for the central testing lab –But not recommended for pivotal trials due to prescreening issues.

Co-development – Idealized scenario



*Clinical validity of the IVD is obtained results of the therapeutic product trial

More realistic scenario:



- High level positive results leads to early phase data used to support the Rx
- Variety of LDTs used to accrue patients
- Dx brought in late
- Scramble to get specimens from trial subjects
- Absence of screen negatives
- Post-hoc, retrospective analyses a game-changer
- Lack of communication between Rx and Dx leaves Dx wondering about anticipated timelines

Clinical Trial Considerations

- Pre-specify primary and co-primary endpoints and prospective-retrospective analyses with the test
- Consider if there is the possibility that phase I/II data will be used for Rx approval and be prepared
- In some cases, there are expectations for evaluating Rx effect in test negatives (e.g., gene signature)
- Pre-specify the inclusion criteria for multiple biomarkers to get analytical claims even if not clinical
- Determine expectations for representation of multiple biomarkers in trial
- Plan to bank Specimens!

Developing a Specimen Acquisition Plan

- Pre-specify the specimen sampling method (e.g., FFPE, FNA); prepare to analytically validate each.
- Bank samples from all patients evaluated for enrollment (Intent-to-diagnose; test negative and test positive)
- Obtain adequate sample volumes for retesting
- Consider policies in foreign countries
- Pre-plan appropriate informed consents in early all-comer phase trials
- Consider obtaining paired specimens if multiple specimen types will be claimed
- Consider impact of storage on specimen/analytes
- Consider pre-planning specimen stability studies (especially for GS and RNA assays-save prototype lots as well)
- Specimen handling protocol locked down (can record protocol deviations)
- Adequate annotation (tumor characteristics, patient characteristics, testing)

Pre-Screening –unable to control the pre-screening

- Short of having a single CTA
  - Try to include a central testing lab as one of the sites (this will enable a large proportion of the testing at a single site and provide test negatives)
  - Have all Labs using the same set of reagents, platform and clinical cut-off
  - Qualify the labs meet a threshold of performance
- Ask clinicians to send some* test negatives forward as well (they may be positive by your test and give the patient opportunity for enrollment)
- *Pre-plan the number of negatives needed for a bridging study

  Meijuan Li, 2015. Journal of Biopharmaceutical Statistics, 25:1–11.
- Collect information about local testing method (technology/reagents, cut-off, test LoD, prevalence of the biomarker(s) in that lab

Bridging Study Basics

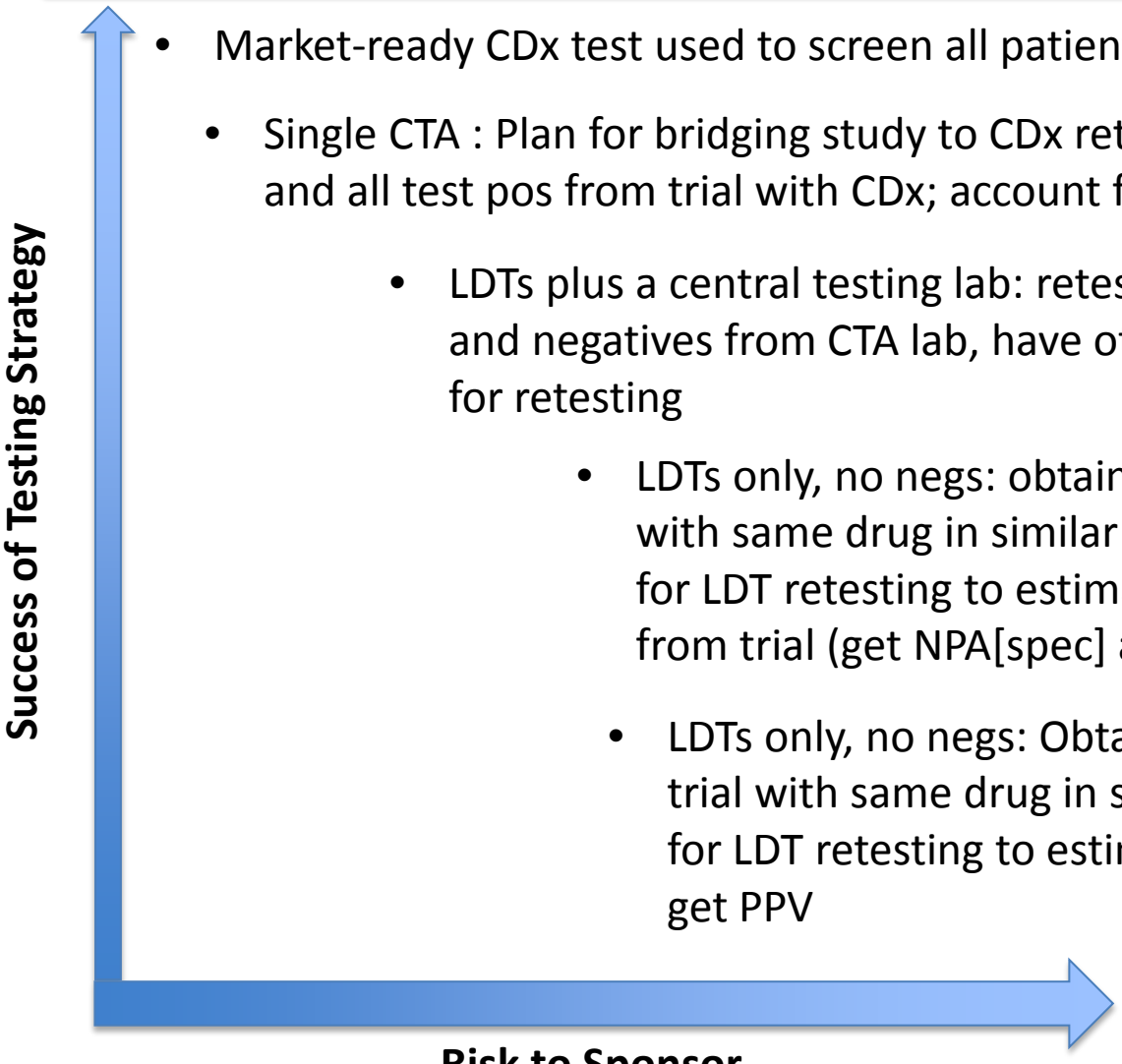
Statistical Plan that takes into account discordance, missing samples and impact on drug efficacy.

- Retest population should be representative of the intended use population for the device.
- Re-analysis of the trial for effectiveness of device is potentially biased if subset not representative.

Sponsor should plan to assess available sample representativeness and incorporate into an analysis plan

- identify variables that have effects on the test result
- identify variables that can impact therapeutic outcomes

Bridging Studies – Options for Missing Negatives



- Market-ready CDx test used to screen all patients
- Single CTA : Plan for bridging study to CDx retest (sufficient*) banked test neg and all test pos from trial with CDx; account for missing specimens in SAS
- LDTs plus a central testing lab: retest all banked positives, and negatives from CTA lab, have other labs send forth some negatives for retesting
- LDTs only, no negs: obtain several LDT neg from *another* trial with same drug in similar population and send to CDx for LDT retesting to estimate discordance and prevalence from trial (get NPA[spec] and prevalence to calculate PPV.
- LDTs only, no negs: Obtain CDx pos from *another* trial with same drug in similar population to send back for LDT retesting to estimate discordance and to get PPV
- Prevalence from literature, procure LDT neg samples from another trial to get NPA (spec)

Avoid turning your validation set into your training set

- If you optimize your CDx based on results of your pivotal trial, you have turned that specimen set into a “training set” which can no longer be considered the “clinical validation set”
- Additionally, analytical validation should be done with the final IVD Test System. Changes may result in analytical studies needing to be repeated.

…worth noting

- Use the CDRH Pre-submission Program for feedback: Include the Q-sub number in communications with CDER/CBER
- Include the BIMO elements in the Modular Shell (can be listed in the shell as coming in as an amendment to the shell or as part of the clinical module)
- Include line data from the clinical trial (Pharma can use master device file process to avoid disclosure to Dx if preferred).
- Accuracy data requested with specimens from clinical trial for genotyping CDx
  - provides real world accuracy
  - establishes performance bar for follow-ons
  - analyses should include invalids
- Not enough analytical data with clinical specimens – expect postmarket conditions of PMA approval
- Inadequate availability of Test - PMCs in Rx approval

New Developments:

- NGS oncopanels for clinical use –working on path forward
- Liquid Biopsies –approved two new CDx for cfDNA
- Follow-on CDx –approved same technology, different technology
- Complementary IVDs –approved three

Additional References:

- Meijuan Li. **Statistical consideration and challenges in bridging study of personalized medicine.** Jour of Biopharm Stat 2015; 25(3):1–11.

- Gene Pennello. **Analytical and clinical evaluation of biomarkers assays: when are biomarkers ready for prime time?** Clinical Trials. 2013;10(5):666-76

Thank you for your time.

Please feel free to email me questions any time.

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