Analytical Validation for IDE Submissions

Sharon Liang, M.D., Ph.D.

Division of Molecular Genetics and Pathology
OIR/CDRH/FDA

June 10, 2016
Rockville, MD
IDE and Genomics Workshop

Disclaimer

The views expressed during this presentation are those of the presenter and do not necessarily reflect the policy or position of the US FDA or the US government.

Presentation Topics

- Basic components of an IDE submission
- Analytical validation studies to be provided in an IDE submission
- Examples of molecular IDE submissions
  - NGS-based oncology panels

Basic Components of an IDE Submission

- Intended Use
- Device Description/controls
- Summary of Prior Investigations
- Clinical Protocol
  - Target population, study sites, numbers of patients being tested
  - How is the device planned to be used
- Analytical data (abbreviated)
- Administrative (elements in the IDE checklist)
  - Investigators agreement/Informed consent/IRB information
  - Manufacturing/Sales Information

Presentation Topics

- Basic components of an IDE submission
- Analytical validation studies to be provided in an IDE submission
- Examples of molecular IDE submissions
  - NGS-based oncology panels

Analytical Validation Studies in IDE

- Analytical validation study design considerations (including pre-analytical)
  - Does it measure the analyte(s) accurately and reliably in the hands of the intended users with various sources of variability?
    - Intended type of clinical specimens
  - What specimen handling is required?
    - Sample type/matrix: Serum, EDTA/Heparin Plasma, Urine
    - Collection /transport/storage: Preservative/stabilizer
    - Preparation: Fixation/sectioning, micro-/macro-dissection
    - Sample stability: Real-time, freeze thaw
      - Especially important for use of archived samples for clinical studies

Analytical data evaluated in IDE comparing to other submissions

IDE

- Analytical accuracy
  - Analytically validated comparator method(s)
- Analytical sensitivity (LoD)
- Precision/reproducibility
  - Performance around cut-off
- Pre-analytical studies
- Analytical specificity (if applicable)

510(k)/PMA

- Accuracy ← Valid comparator
- Sensitivity/Linearity (LOB/LOD/LOQ)
- Precision (Repeatability/Reproducibility)
- Specificity (Exclusivity/Cross Reactivity /Interference)
- Guard band studies/robustness studies
- Matrix/Method/Instrument Equivalency (Serum vs plasma, method comparison, etc)
- Stability (test, calibrators, controls)
- Others

Both quantity and quality of studies are different

Presentation Topics

- Basic components of an IDE submission
- Analytical validation studies to be provided in an IDE submission
- Examples of molecular IDE submissions
  - NGS-based oncology panels

NGS-based Oncology Panels

- Single Test, Multiple Biomarkers, Multiple Indications
  - One panel can be used for multiple indications
  - Challenges the regulatory paradigm for Companion Diagnostics
    - Clinical validity, analytical validity, robust across tissue types
- Special issues with NGS
  - Potential to detect rare and novel variants
  - Rapidly evolving technology
  - Challenges for NGS-based test analytical validation
    - Unit of validation – specimen source, analyte type, specific gene variants, specific exons, variant categories, genomic landscape
    - Lack of comparator methods and reference materials
    - Rare specimens
    - One platform may have different uses (SNVs/indels/CNVs; Germline vs. somatic)

Analytical data to be provided in an IDE

1. Analytical Accuracy
   - Sample panel
     - Representative of Variants (types, genomics context (GC contents, repetitive regions, etc.))
     - Clinical sample is preferred
     - Cell lines are acceptable with sufficient justifications/experimental evidence
   - Reference methods or well-characterized samples (e.g. HapMap DNA)
     - Identify reference method for each variant type
     - Pre-specify quality metrics for reference methods
   - Results:
     - Per sample, per variant/variant type
     - % agreement (OPA, PPA, NPA across all bases sequenced and per variant)

Analytical data to be provided in an IDE

2. Precision/Reproducibility
   - Sample panel
     - Variants (types, genomics context (GC contents, repetitive regions, etc.))
     - Specimens
       - Tumor types (if no separate sample handling study)
       - Tumor content/allelic burden
   - Sample size
     - Sufficient number for each variant type/genomic context
   - Runs/instrument(s)
   - Results:
     - Per sample, per variant/variant type
     - % agreement (OPA, PPA, NPA across all bases sequenced and per variant)

Analytical data to be provided in an IDE

3. Limit of Detection (LOD)
   - DNA input
   - Tumor content
   - Mutant allele frequency of variants (by variant type)
4. Pre-analytical (sample handling, matrix comparison)
   - Tumor types (blood, breast, lung)
     - For solid tumors, justify why certain tumors are chosen for validation
     - Demonstrate that different tumor types give comparable DNA quality
   - Sampling methods (core needle, etc.)
   - Storage (FFPE, FF)
   - If FFPE is the sample type, but cell line is needed to cover some variants, FFPE cell lines need to be used

Challenges with Analytical Validation

- Specimen handling variability
- Difficulty obtaining clinical samples for rare alleles
- Multiplex assays often require complex validation
- Lack of reproducibility/high analytical variability
- Analytes are not stable
- Lack of comparators, calibrators and standards
- Whole genome technologies present unique challenges to validation strategies

Summary

- Only variants that will be used in the clinical trial need to be validated in the IDE
- Representative of variants and samples can be used to validate NGS-based tests
- Analytical validation data to be submitted in IDE
  - Accuracy
  - Limit of Detection (LoD)
  - Precision/reproducibility
  - Pre-analytical studies
  - Analytical specificity (if applicable)
- Early interaction with the Agency is extremely helpful
  - Pre-submission process
  - Guidance www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Thank you!

Sharon Liang
Sharon.Liang@fda.hhs.gov

Device Description

- Detailed descriptions of the device
  - What components does it have? (e.g., NGS-based test)
    - Platform/specimen type
    - Genes and genomic regions, types of variants (e.g. base substitution, indel, fusion, CNV)
    - Depth of coverage
    - Algorithm (used for assigning treatment arms, for accepting a variant call)
  - How does it work to generate a result?
  - What are the limitations of the technology?
  - Does it include software?