Molecular Diagnostics 510(k) Submissions

AMDM/FDA – OIVD 510(k) Workshop
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Division of Chemistry and Toxicology Devices
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Molecular Diagnostic Tests

A large and growing part of clinical diagnostic testing in the US

Development of genetic tests that detect

- disease, risk of disease
- disease prognosis
- response to therapy
- likelihood of adverse event/appropriate dosing
- Infectious disease

Genetic signatures for diagnosis/prognosis/prediction

- Common complex diseases
- Subclassification of disease
- Therapeutic choice

Molecular Diagnostic Tests

FDA is concerned that molecular diagnostic tests be reliable and that patients and health care professionals understand both the value and the limitations of such testing

Agenda

- Performance Information
  - Preanalytical/Analytical Validation
  - Clinical Validation
  - Recurring issues
  - New issues
- RUO/Reagents/Instruments
- Personalized Medicine
- Mock 510(k) exercise
- Submitting your molecular diagnostic device

Test Performance

Analytical validity of the test(s):

- Does my test measure the analyte(s) I think it does?
- Correctly?
- Reliably?

Clinical validity of the test(s):

- Does my test result correlate with the expected clinical presentation?
- How reliably?

Analytical Performance

Precision / Reproducibility

- 3 sites
- Adequate coverage of all genotypes/tumor types
- Use clinical samples
- Include pre-analytical steps (e.g., extraction/purification)

Accuracy

- Real clinical samples
- Cover all possible genotypes, subtypes/classes
- Compare genotyping to Bi-directional sequencing
- Expression tests compare to clinical diagnosis

Limit of Detection

- Lowest and highest concentration of input sample

Potential Interferences

- Co-administered drugs
- Pre-analytical test components (e.g., extraction buffer)
- Common endogenous and exogenous substances

Challenges for Analytical Validation

Genetic tests:

- Samples of rare alleles difficult to find
- Tests that evaluate a panel of alleles using complex algorithms often require complex validation
- Bi-directional sequencing is the comparator – can be difficult for somatic mutations, deletions, translocations

Genomic/Proteomic tests:

- Analytical variability is an issue (Sometimes pre-analytical)
- No analytical gold standard for comparison
- QC and standards may not exist

Clinical Validation

- Clinical studies to validate molecular diagnostic test often have unique statistical challenges
- Pre-specified clinical/statistical analysis plan is crucial
- Expression Patterns, Proteomic patterns, or Genetic Algorithms should be pre-specified, developed in one data set, “locked,” and confirmed in an *independent* data set (training set and validation set, respectively)

The pivotal validation study must investigate test use in the claimed clinical population using the final test configuration!

Clinical Performance

- Retrospective studies OK? Yes – *IF*:
  - the study supports the intended use of the test
  - samples were collected and stored appropriately
  - no sampling bias

- Literature to support device
  - Should be analyzed, summarized, organized
  - All published studies are not created equal!
  - (Note: Submit as if you are making the case for your device)

Pitfalls of Retrospective Samples

- Only looking at cases with a minimum follow-up….biased estimates of survival
- Avoiding any censored cases
  …biased estimates of survival
- Looking from current samples backward
  …May be biased compared to prospective look
- “Convenience samples”…may not accurately reflect IU population
- Samples may not survive extended time in freezer
- Practice changes, e.g., new drug regimens, may limit usefulness

Challenges for Clinical Validation

- Microbiology Background positives (non-infection)
- Sample availability
- Multiplex detection/regulation

Most frequent issues…

- Lack of samples covering all genotypes
- Lack of literature to support validity
  - One or two references may not be sufficient
- Pre-analytical issues
- Sample matrix issues

What is the utility for rare polymorphisms considering their low frequency in the population and the sparse literature available?

New issues…

Lack of reference method

- Validated RT-PCR method to detect hMPV RNA in clinical specimen

Adding a new analyte to a multiplex assay

- Cannot treat the addition of the analyte as if it is a stand alone assay
- Must demonstrate how well the assay now functions *in toto*
- Re-establish the clinical and analytical performance of the previously cleared analytes in the new assay configuration

Research Use Only (RUO)

RUO instruments/reagents - regulatory status:

- Labeled as "*for research use only, not for use in diagnostic procedures* "
- Not reviewed by FDA
- Not manufactured under Quality System Regulations
- Not subject to Medical Device Reporting
- Not Registered and Listed

RUO Device or Device with RUO component =

No assurance of safety & effectiveness regarding test result

RUO tests should not be promoted or sold for clinical use

Reagent Considerations

Be sure that reagents for use with your platform are for IVD use (not labeled RUO)

General Purpose Reagents (GPRs - 21 CFR 864.4010) – meant to be reagents that do not require instructions for use, except storage, mixing, etc. (e.g., Tris buffer, MgCl, etc.)

Note: collection kits and extraction kits are not GPRs

Nucleic Acid Extraction kits:

- Should be validated with the assay(s)
- Should be listed under 21 CFR 862.2310
  [Clinical Sample concentrator (Class I, exempt, GMPs required)]

Nucleic acid sample collection kits:

Are regulated by type-

- With preservation/stabilization functions under 21 CFR 862.1675
  [Blood specimen collection device (Class II)]
- Passive collection under 21 CFR 864.3250
  [Specimen transport and storage container (Class I, exempt)]

RUO-labeled materials create challenges for clearance/approval

Instrument Considerations

Be sure that instruments for use with your test are for IVD use (not labeled RUO)

- General Purpose Equipment (21 CFR 862.2050)
  - meant to be basic equipment
  (e.g., balances, pipettes, pipette tips, etc.) but not instruments
  - Users with general laboratory training can operate
  - do not contain interpretive software

- Instruments have separate regulations by type
  - Many IVDMIA platforms may be classified under 21 CFR 862.2570
  [Instrumentation for clinical multiplex test systems (Class II)]

RUO-labeled instruments create challenges for clearance/approval

Personalized Medicine

Drug/Dx Co-development / Companion Diagnostics

Advantages:

- Identify patient populations in which a drug is most effective
- Avoid dangerous side effects in certain populations
- Rescue a failed trial / new drug
- Mechanistically link a treatment to the disease

Challenges:

- Timing
- Regulatory path
- Science/Knowledge base
- Trial design

Personalized Medicine

Drug/Dx Co-development / Companion Diagnostics

- A companion diagnostic (CDx) is a biomarker test that is *required* for correct use of a therapeutic (part of drug labeling)
  - In US requires FDA approval of both
- Biomarker may be “recommended” in the drug labeling
  - to provide extra information
- But….. if the test doesn’t work, how can you use drug correctly?

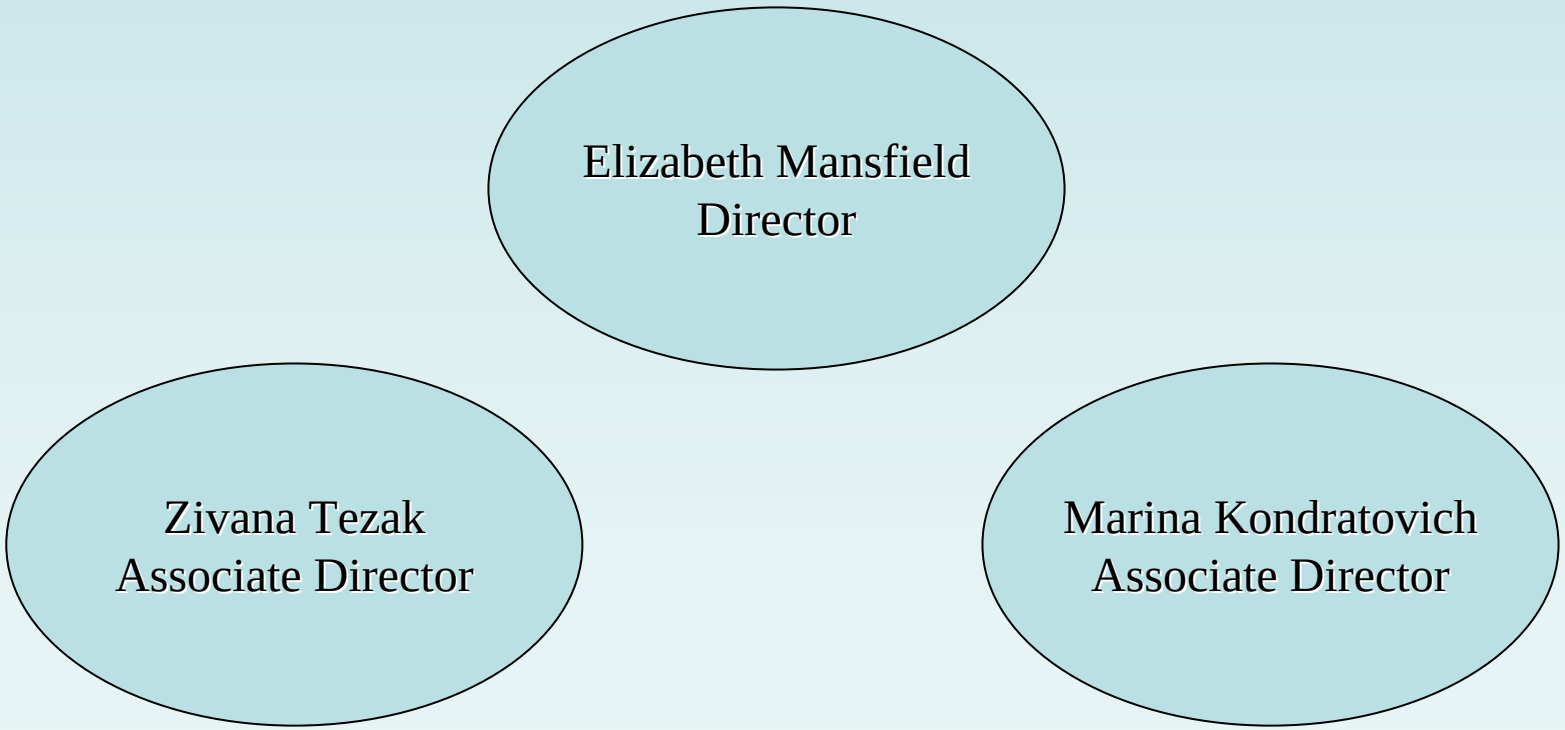
Personalized Medicine

Drug/Dx Co-development / Companion Diagnostics

- Standardize your assay platform as early as possible
  - Hardware and software
  - If you cannot, bridging studies will be needed
    - samples from Phase 2 and 3 studies should be stored for use in any bridging studies that might be necessary
- BEFORE Pivotal (Phase III) Trials Begin Assay should be fully verified
  - all reagents, instrument, software, assay outputs, algorithm, etc.

Personalized Medicine

New Personalized Medicine staff within OIVD:



Mock 510(k)

- Exercise between OIVD and NCI
- Two submissions:
  - Multiplex MS-based breast cancer diagnostic test
  - SDIA- Immunological Array platform for simultaneous assay of multiple glycoprotein isoforms associated with tumor metastasis

- Published in Clinical Chemistry, Feb. 2010

(Regnier, F.E., et al, Clin Chem 2010 56: 165-171.)

Resources: Guidance Documents

- Pharmacogenetic Tests and Genetic Tests for Heritable Markers
- Drug-Diagnostic Co-Development Concept Paper
- Drug Metabolizing Enzyme Genotyping System - Class II Special Controls Guidance Document
- Instrumentation for Clinical Multiplex Test Systems - Class II Special Controls Guidance Document
- Gene Expression Profiling Test System for Breast Cancer Prognosis - Class II Special Controls Guidance Document
- Cardiac Allograft Gene Expression Profiling Test Systems – Class II Special Controls Guidance Document
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices

Resources: Guidance Documents

- Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable
- In Vitro Diagnostic Multivariate Index Assays – Draft Guidance
- Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions
- In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions
- Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

Resources: Decision Summaries

- Roche AmpliChip CYP450 Test

  http://www. accessdata.fda.gov/cdrh_docs/reviews/K043576.pdf

  http://www. accessdata.fda.gov/cdrh_docs/reviews/K042259.pdf
- Tm Biosciences Tag-It Cystic Fibrosis Kit

  http://www. accessdata.fda.gov/cdrh_docs/reviews/K043011.pdf
- Third Wave Technologies UGT1A1 Assay

  http://www. accessdata.fda.gov/cdrh_docs/reviews/K051824.pdf
- Verigene Warfarin Metabolism Nucleic Acid Test

  http://www.accessdata.fda.gov/cdrh_docs/reviews/K070804.pdf
- Affymetrix GeneChip Microarray Instrumentation System

  http://www.accessdata.fda.gov/cdrh_docs/reviews/K042279.pdf
- Agendia MammaPrint Assay

  http://www.accessdata.fda.gov/cdrh_docs/reviews/K062694.pdf
- XDx AlloMap

  http://www.accessdata.fda.gov/cdrh_docs/reviews/K073482.pdf
- Luminex xTAG Respiratory Viral Panel

  http://www.accessdata.fda.gov/cdrh_docs/reviews/K063765.pdf

Regulatory Process

How can the regulatory process for molecular devices be facilitated?

Communication!

Sponsors should discuss their device with CDRH as early as possible to work out:

- Regulatory path (classification, de novo, etc…)
- Analytical and Clinical Data requirements

Regulatory Process

A “Pre-IDE” should be used to discuss molecular devices prior to starting studies or submission

- Pre-IDE submissions allow for informal communication between CDRH and sponsors
- During a Pre-IDE, CDRH can give feedback on analytical studies for test validation and information required for clinical validation
- Test-specific challenges can be discussed prior to the start of validation studies

White Oak Campus

Questions?

Ask Us!

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