Regulatory Considerations for US FDA Submissions for Companion Diagnostic Tests

W. Jeffrey Allard, Ph.D.
President
Lakeside Life Science, LLC

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“An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.”
Definitions

➤ Analytical Validation/Verification
   Verify assay meets its Specifications (TPP)

➤ Validation
   Test is fit for its Intended Use
   Clinical Validity vs Clinical Utility

➤ Predictive vs Prognostic
   Prognostic: More general outcomes
   Predictive: Predicts response to specific treatment

➤ Companion Dx vs Complementary Diagnostics

➤ Studies: Observational vs Interventional
   IDE requirements - Significant Risk / NSR
FDA Regulation of IVDs

➤ **Class I:** Exempt from submission
  GMP and Device Registration

➤ **Class II:** Two options
  - Traditional 510(k): Comparison to “Predicate Device”
  - De Novo: Class II but demonstrate S&E

➤ **Class III:** PMA
  - Safety and Effectiveness
  - Manufacturing (QMS)
  - Mandatory Pre-approval Manufacturing Audit

➤ **Today:** Risk Based – Approximately!
A Philosophy of Successful FDA Interactions

➤ What does FDA Want?
A: Good Science and Good Medicine
  Regulations are secondary

➤ When and how to ask for guidance
When: At the beginning; if you have a question
How: State the case and ask for agreement
Just ask? In general No. Unless regulatory.

➤ Presubmission Process – Logistics
Meetings: 60-90 days
Written comments: 3 days prior to meeting
Meeting may be cancelled or conference call
Laboratory Developed Tests

➤ Origin of the species as we think of LDTs today
  Oncotype Dx, Genomic Health
➤ Status and future of FDA regulation of LDTs
  Guidance?
  FDA regulation vs CMS or other?
  Role of Congress
  Future of LDT regulation
➤ LDTs as Companion Dx
  Is this a viable regulatory approach?
  Limitations
Regulation of Companion Diagnostics

➤ Joint vs separate CDx development

➤ Combination Product: Possible but unlikely

➤ Companion vs Complementary: Regulatory
  Companion: Class III PMA, S&E
  Complementary: Same!
  Could a Complementary test be a Class II?
    Possibly – Prognosis vs Prediction

➤ Comparison study vs S&E
  You can do it, but it’s a PMA!
  Example: P100027-Ventana INFORM HER-2
## NGS CDx Regulatory Considerations

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<th>Test</th>
<th>Regulatory Pathway</th>
<th>Instrument</th>
<th>Comments</th>
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<td>ThermoFisher</td>
<td>Oncomine Dx</td>
<td>Class III PMA</td>
<td>Ion PGM Dx</td>
<td>Priority Review, Breakthrough technology</td>
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<tr>
<td>MSKCC</td>
<td>IMPACT</td>
<td>Class II De Novo</td>
<td>Illumina HySeq</td>
<td>LDT with 10,000 patient database</td>
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<tr>
<td>Foundation (Roche)</td>
<td>F1CDx</td>
<td>Class III PMA</td>
<td>???</td>
<td>LDT</td>
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CDRHs Approach to tumor Profiling NDS Tests

- CDx
- Cancer Mutations with Evidence of Clinical Significance
- Cancer Mutations with Potential Clinical Significance

Evidence
Recent FDA CDx NGS Approvals
Oncomine Dx

A qualitative in vitro diagnostic test using NGS to detect SNVs, deletions in 23 genes from DNA and fusions in ROS1 from RNA in FFPE tumor tissue samples for non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System.

The test is indicated to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1. List of variants for therapeutic use (N=3)

Safe and effective use has not been established for selecting therapies using this device for the variants in Table 1 in tissue types other than NSCLC.

Analytical performance using NSCLC specimens has been established for the variants listed in Table 2.

Table 2. List of variants with established analytical performance only (N=4)
qualitative IVD for targeted next generation sequencing of FFPE tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.
Recent FDA CDx NGS Approvals
FoundationOne CDx™ (F1CDx)

NGS for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA from FFPE tissue. intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. single-site assay....

Table 1: Companion diagnostic indications NSCLC, Melanoma, Breast cancer, Colorectal cancer, Ovarian cancer
Regulatory Considerations for US FDA Submissions for CDx Tests
Panel Discussion

W. Jeffrey Allard, Ph.D., Lakeside Life Science
Debra Rasmussen, Janssen
Aaron Schetter, Ph.D., M.P.H., FDA, CDRH
Julie Engel, Celgene
William Pignato, WJ Pignato & Associates
# PMA vs De Novo

Three recent CDx approvals:

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<th>Oncomine</th>
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<td>F1CDx</td>
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CDx now have two regulatory pathways:

1. Important differences in requirements
2. Involvement of NYS in De Novo applications
3. Advantages
4. Limitations
5. Applications to new drug trials
6. Analytical Verif/Valid study requirements
Companion Dx vs Complementary

1. Claims for mutations and level of clinical significance vs claims of drug efficacy?
2. Are they regulated differently? How?
3. Complementary Diagnostics: An escape hatch for implementation of Personalized Medicine?
Laboratory Developed Tests

1. Can an FDA-approved/cleared CDx test be an LDT?
2. Advantages and limitations of LDTs vs traditional test kits
3. Will FDA regulate LDTs in the future and in what manner?