FDA Industry IVD Roundtable

Personalized Medicine Update

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May 30, 2014
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The latest on…

- Office Reorganization
- Working Groups
- Guidance Documents
- Next Generation Sequencing FAQs

Convergence of Staff: Molecular Product Review and Policy Analysts

Deputy Director, Personalized Medicine

Elizabeth Mansfield

Personalized Medicine Staff

Molecular Genetics and Pathology Devices

Division Director: Reena Philip

Marina Kondratovich

Zivana Tezak

Pamela Bradley

David Litwack

Molecular Pathology and Cytopathology

Yun-Fu Hu

Molecular Genetics Branch

Donna Roscoe

Ongoing Working Groups

Drug-Device Co-Development

- Doubling annually; Developed Tracking process
- Across Centers and Offices; maturing definition of CoDx
- Draft Guidance - In Vitro Companion Diagnostic Devices [Final under review]
- Draft Guidance - Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product [working title – under review]

"Me-Too" Companion Diagnostic Working Group

- Investigating statistical approaches for second generation and new companion diagnostics
- Handling missing data with statistical assumptions very challenging; for example
  - Missing samples
  - Missing trial outcome
  - Missing prevalence based discordance between two tests
- Follow Center Strategic Initiatives - Consideration for opportunities for post-market evaluation

Investigational IVDs in Rx Trials

- Subject to the Investigational Device Exemption (IDE) regulation 21 CFR Part 812 …
- Addressing challenges with two regulatory paths
- Developing risk-assessment basis for SR vs NSR decisions for investigational diagnostics in therapeutic trials
- Pre-submission process for Risk determination requests
- Draft Guidance - Investigational IVD Devices Used in Clinical Investigations of Therapeutic Products
  [working title – final review]

Reference Material Project with NIST

- First Reference material (NA12878): well characterized genomic DNA across multiple platforms
- Due to be released within the month

LDT Guidance

–currently under administrative review

Working group – Next Generation Sequencing

Need: GMP manufactured NGS instruments, software and reagents for assay development

Solution: Create a regulatory path for next generation sequencing instruments and reagents without specific indications

- **High Throughput Genomic Sequence Analyzer for Clinical Use** Class II -21 CFR 862.2265 (exempt from the premarket notification requirement subject to the limitations in 21 CFR 862.9)
- **Reagents for Molecular Diagnostic Test Systems** Class I -21 CFR 862.3800

High Throughput Genomic Sequence Analyzer for Clinical Use Class II -21 CFR 862.2265

The **Labeling** for the instrument system must include descriptions of, and validation on the instrument for:

- Pre-analytical and analytical reagents
- The legally marketed analytical software that includes sequence alignment and variant calling functions.
- Specimen type(s) and the type(s) of nucleic acids (e.g., germline DNA, tumor DNA).
- The type(s) of sequencing (e.g., targeted sequencing) and sequence variations (e.g. single nucleotide variants, insertions, deletions)
- The appropriate read depth for the sensitivity claimed
- Various Limitations that specify the types of sequence variations that the instrument cannot detect with the claimed accuracy and precision (e.g., insertions or deletions larger than a certain size, translocations).
- Performance Characteristics

Working group – Next Generation Sequencing (NGS)

- Need to develop efficient approaches for analytical validation of NGS / highly multiplexed genetic tests
- Continue to developing regulatory strategies for multiplex assays; particularly cancer panels
- Looking at possible mechanisms to approve IDEs for sites conducting NGS clinical testing for Rx trials
- Supporting database development

Next Generation Sequencing (NGS) FAQs

Does clearance of the Illumina MiSeq platform mean any assay run on it is validated?

- No, the MiSeq was not cleared or approved with a specific indication, assays should demonstrate validation for the indication(s).

Can I use the Illumina MiSeq as a reference method for accuracy of my sequencing assay?

- Yes, provided the MiSeq is validated for that allele and includes pre-specified quality metrics.

Next Generation Sequencing (NGS) FAQs

If I use NGS in my clinical trial do I still need to provide analytical validation to the FDA?

- Depends. The requirement for FDA to review your analytical validation is dependent on whether an IDE is needed for use of the device in the clinical trial (based on risk/safety) and/or whether CDER/CBER believe a demonstration of analytical validation is necessary to support conclusions from the trial (based on concern over whether study may fail to meet its objectives).

Looking Forward

- More hires with necessary expertise
- Experiential Learning Program – Opportunity for Industry and Laboratories to provide FDA reviewers with on site demonstrations of processes
- Several workshops intended to get stakeholder input