Advancing Quality and Regulatory Science in the CDRH Office of In Vitro Diagnostics and Radiological Health

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Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

MDIC Case for Quality Forum
February 25, 2019
Or,

What I’ve learned after 7 months on the job...
Very Talented, Dedicated Staff

- ~290 Scientists & Engineers
  - ~21 MDs
  - ~153 PhDs
  - ~46 Masters

Note: Numbers are approximate and include open headcount
Numerous Very Important Tasks

OIR Activities "50k Foot View"

Policy
- Rulemaking
- Guidance
- Standards
- SOP/WI
- Device Determination
- Specific Topics: CRM, MMA, Dig Health, LDI

Outreach/Comm.
- Public/Media Requests
- Meetings with Industry
- ELP
- Comm. Planning

Special Projects
- Agency Initiatives
- Center Priorities
- Office Projects

Admin Support (PMO)
- Budget/Payroll
- HR (Hire, PMAP, etc.)
- Timekeeping
- Awards
- Employee Requests
- Purchases/Supplies
- Travel
- Conference/Training
- Other

Quality Management
- Consults

Similar to other offices

Premarket
- 510(k)
- Third Party Oversight
- 513(g)
- De Novo
- EUA
- IDE
- Expanded Access
- Master File
- Pre-EUA
- PMA/Mod-PMA
- Q-Sub (Pre-Sub, etc.)

Cross Program
- Intake/eCopy
- User Fees
- Int. Reviews (RTA, SI)
- Reporting to Industry
- Comp. Product/IOC
- Appeals
- Manage Product Codes

Food Drug and Cosmetic Act (FDCA)
- FDA

Compliance
- Complaints
- EIRs
- Imports
- Recalls

Surveillance
- PAS
- MDR
- PSS/S22
- Signal Mgmt.

EPRC
- Premarket (EPRC)
- Intake
- Product Reports
- Exemptions
- Variances
- Complaints
- EIRs
- Imports
- recalls
- Compliance Actions (Notification Letters, etc.)
- ARO

Radiation Control for Health and Safety Act of 1968 (now in FDCA)

MOSA
- Accreditation Bodies
- States as Certifiers
- Inspect/Certify Facilities
- Compliance (Complaints/Oversight)
- Reporting and Comm.
- Maintain Data Systems

Mammography Quality Standard Act (MQSA)

Similar to ODE

Similar to OCB

Similar to DOE

CR
- CW
- Clinical Laboratory Improvement Amendments (CLIA)
Highly Productive

• 1,760 OIR Submissions in 2017
  – 126 PMAs and PMA Supplements
  – 743 510(k)s
  – 848 Pre-Submissions
  – 43 IDEs
  – Plus multiple other types of submissions
MDUFMA Reports

Agenda and Materials

- May 8, 2015 MDUFA III Performance Report (PDF - 2.9MB)
- February 2, 2015 FDA MDUFA III Performance Report (PDF - 1.9MB)
- November 18, 2014 FDA MDUFA III Performance Report (PDF - 1.2MB)
- July 29, 2014 FDA MDUFA III Performance Report (PDF - 10.3MB)
- April 28, 2014 FDA MDUFA III Performance Report (PDF - 10.2MB)
FY2018 Highlights

• Finalized two NGS guidance documents, “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics” and “Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based *In Vitro* Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases”.

• Approved the first fully implantable device to measure glucose in people with diabetes.

• Published a plan for “Eliminating Routine FDA Re-review of Third Party 510(k) Reviews” and a “Draft Guidance on the 510(k) Third Party Review Program”.

• Granted first DNA-based test for minimal residual disease for hematologic malignancies (NGS).

• Multiple Breakthrough Device Designations
YTD FY2019 Highlights

• Published both “Recommendations for Dual 510(k) and CLIA Waiver by Application Studies” and “Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices”
• Published “Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices”
• Published “Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products”
• Published “Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use” and "Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use”
• First Genetic Database Recognized
• Granted first interoperable insulin pump
• Granted first Mycoplasma genitalium Assay
• Granted first FISH assays for chromosomal abnormalities in patients with hematologic malignancies
• Granted first Human Milk Analyzer
CDRH Reorganization: Office of Product Evaluation and Quality
Total Product Lifecycle (TPLC) Reorganization

- Foster organic connections within the organization
- Streamlined decisions and processes
- Shared priorities
- Better customer service
- Professional growth
## Future OPEQ Offices

<table>
<thead>
<tr>
<th>OHT</th>
<th>Scope of Products / Responsibilities</th>
<th>Office Director</th>
</tr>
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<tbody>
<tr>
<td>OHT 1</td>
<td>Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices</td>
<td>Malvina Eydelman, M.D.</td>
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<tr>
<td>OHT 2</td>
<td>Cardiovascular Devices</td>
<td>Bram Zuckerman, M.D.</td>
</tr>
<tr>
<td>OHT 3</td>
<td>Reproductive, Gastro-Renal, Urological, General Hospital Device and Human Factors</td>
<td>Ben Fisher, Ph.D.</td>
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<td>OHT 4</td>
<td>Surgical and Infection Control Devices</td>
<td>Binita Ashar, M.D.</td>
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<td>OHT 5</td>
<td>Neurological and Physical Medicine Devices</td>
<td>Carlos Pena, Ph.D.</td>
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<tr>
<td>OHT 6</td>
<td>Orthopedic Devices</td>
<td>Raquel Peat, Ph.D., MPH</td>
</tr>
<tr>
<td>OHT 7 /OIR</td>
<td>In Vitro Diagnostics and Radiological Health</td>
<td>Tim Stenzel, MD, PhD</td>
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<tr>
<td>ORP</td>
<td>Programmatic oversight for premarket, postmarket and compliance activities</td>
<td>CAPT Sean Boyd</td>
</tr>
<tr>
<td>OCEA</td>
<td>Programmatic oversight for clinical trial, BIMO, RWE, and statistical activities</td>
<td>Owen Faris, PhD</td>
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A little about me...

• Duke - MD/PhD, Pathology Residency, NIH & Clinical Molecular Genetics Fellowships

• Duke Pathology Faculty 1997-2003
  – Opened Clinical Molecular Diagnostics Lab (1997)
  – Medical Director, Clinical Cytogenetics
  – Flow Cytometry, Clinical Staff

• Industry
  – Vysis/Abbott Molecular 2003-2007
  – Asuragen, Austin, TX 2007-2009
  – Quidel, San Diego 2009-2014
  – Invivoscribe, San Diego 2014-2018
Mission, Vision and Values

• Protect and promote public health
• Assure patients, providers and laboratorians have timely access to safe, effective and high-quality medical devices
• Advance regulatory science
• Science-Based decisions
• Innovation, Honesty, Integrity, Accountability, and Transparency
In Vitro Diagnostics in the Age of Precision Medicine

Traditional testing

Next generation sequencing
Developing a Nimble Regulatory Approach for Genomic Tests

**Vision:** Implement new regulatory policies to promote research and accelerate the translation of precision medicine technologies into treatments that benefit patients.

**Goal:** Improve regulatory efficiency; encourage and speed innovation
FDA’s Vision for Regulation of NGS-Based IVDs for Diagnosing Germline Diseases

• **Technical/analytical standards for NGS**
  - Test developers that meet these standards may not have to submit a premarket submission to the FDA.
  - Standards would be developed with the scientific community, and can be updated as science and technology advance.

• **Use of FDA-recognized databases to provide clinical evidence**
  - Use databases as information sources to support the link between genetic variation and health/disease.
  - Test developers may be able to use such databases in support or in lieu of traditional clinical studies.
Analytical NGS Guidance

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases

- Scope: germline WES or panels
- Makes a series of technical recommendations for how NGS-test developers can design and validate their tests
- Accommodates different test designs, components, indications, etc.
- Validation – performance characteristics, evaluation studies
- Labeling recommendations
- Can form the basis for future FDA-recognized standard(s) (e.g., CLSI, ISO) and/or special controls
- Discusses potential for an expedited path to market for tests that meet these standards
Genetic Database Guidance

*Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics*

- **Scope:** publicly accessible databases of genetic variants
- **Recommendations for administrators of databases to demonstrate that the database can be considered a source of “valid scientific evidence”**
- **Voluntary database recognition pathway (similar to standards recognition)**
- **Evidence from databases could support the clinical validity of NGS-based tests**
Key Take Aways

- These two final guidances represent part of FDA’s approach to reviewing innovative and rapidly evolving technologies in a least burdensome manner.
- The analytical guidance arms developers with insight on ways to validate their tests and provides a potential expedited path to market.
- The database guidance enables test developers to harness crowd-sourced data to support the clinical validity of their tests.
Improving 3rd Party Review Program

• Program Challenges:
  • Poor quality submissions that often require re-review
  • Limited public information makes review difficult

• Plans to Strengthen Program:
  • Issued draft guidance on recognition of third parties and a strategy for not routinely re-reviewing 510(k)s reviewed by a third party on September 13, 2018
  • Increase program staff from 1 to 5 FTEs
Codevelopment Guidance

- July 2016: “Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product” draft guidance published
- Intended to be a “How To” for Codevelopment
  - described points to consider in both therapeutic and diagnostic development programs
  - described FDA preferences for certain elements
  - does not prescribe any particular development pathway
- Have received comments and working on finalizing
Clarifies that IVDs used in clinical investigations are subject to the IDE regulation.

Assists sponsors and IRBs in determining the risks of the use of an investigational IVD.

Defines the responsibilities of sponsors and IRBs in complying with the IDE regulations.

Provides FDA’s recommendations and requirements for submitting an IDE application, when required.

We are working on finalizing
Oncopanels

• FDA laid out a clear, defined pathway in a white paper published to our website in the Fall of 2017

• This pathway explains the different levels of evidence needed for different levels of claims for NGS-based oncopanels

• Three Key Submissions Authorized:
  • ThermoFisher’s OncoMine Target Test Dx
  • MSK-IMPACT-De Novo set up Class II pathway, potential 3rd party review
  • Foundation Medicine’s F1CDx-PMA Parallel Review (FDA approval/CMS coverage)
Community Support and Scientific Advancement

OIR is helping to further advance science by:

– Facilitating and participating on Reference Sample Development Efforts
– Developing and supporting precision FDA Standards Participation
Cancer Genomic Somatic Reference Samples

**Goal:** Develop reference samples that can be made available to the public to improve the accuracy, reliability and transparency of NGS-based oncology tests.

**Impact:**

- Aid in efficient NGS test development and validation
- Streamline and possibly obviate steps in the regulatory process for diagnostic companies
- Provide transparency
- Compress development timelines for targeted therapeutics developers

www.fda.gov
Reference Samples and Possibilities

- Develop, characterize, make publicly available **NGS reference sample sets**
  - Characterization efforts; generating “truth sets”
- Community effort – reference sequence
  - Sequence deposition on easily **accessible platform**
    - Integrate calls
    - Develop constantly **evolving “truth” sequence**
    - Metadata explains technical characteristics
  - Characterized samples available
  - Sequence and metadata available

**precisionFDA – platform**, can be used to analyze, integrate and compare data sets
precisionFDA provides...

- Community
- Resources
- **Challenges**
- Expert of the month / Q&A
- A library of reference samples, tools, etc. including community contributions such as:
  - GA4GH VCF comparison tool
  - BWA-MEM mapper
  - GATK 3.5 licensed to precisionFDA
  - VarSim simulator
  - NA12878 NIST, Garvan, and Platinum Genome sequences
- Allows for ease of use, transportability and consistency in performance across platforms

**Members include...**

- NGS-based test providers
- Standards bodies
- Pharmaceutical & biotechnology companies
- Healthcare providers
- Academic medical centers
- Research consortia
- Government agencies

A research roadmap for NGS informatics
Science Translational Medicine, 2016 Apr20, PMID 27099173
precisionFDA challenges

Major focus: reliability and accuracy of NGS bioinformatics pipelines
Questions?