OIR Update

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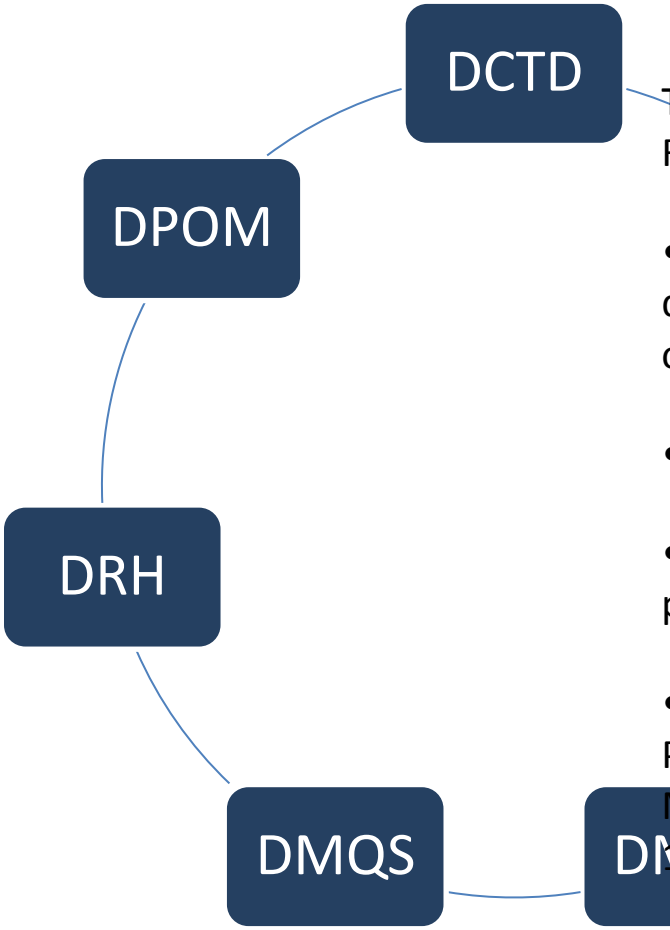
FDA-Industry IVD Roundtable
FDA White Oak Campus

Office of In Vitro Diagnostics and Radiological Health



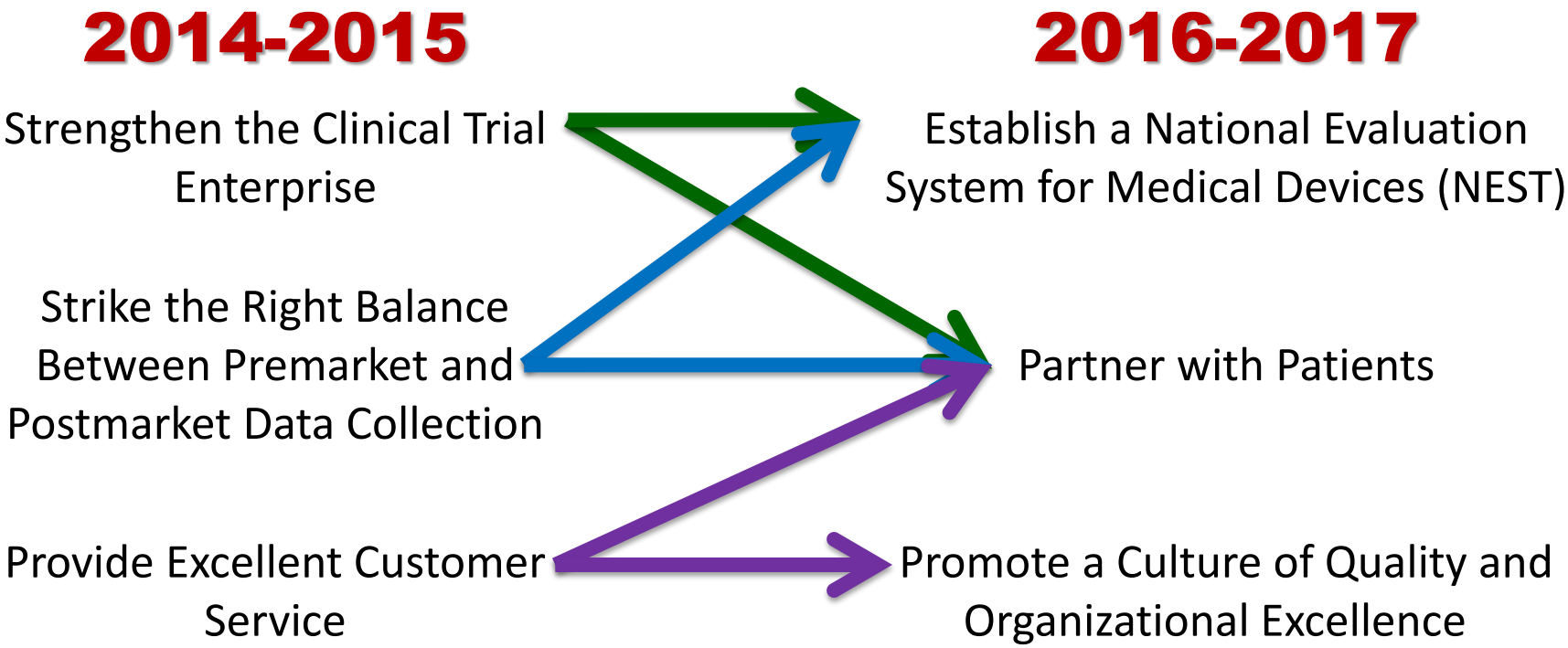
The Office of In Vitro Diagnostics and Radiological Health (OIR):

- regulates in-home and laboratory diagnostic tests (in vitro diagnostic devices, or IVDs);
- regulates radiological medical devices;
- regulates radiation-emitting non-medical products; and
- implements the Mammography Quality Program authorized by the Federal Mammography Quality Standards Act of 1992.

Vision

“Patients in the U.S. have access to high-quality, safe and effective medical devices of public health importance first in the world.”

CDRH Strategic Priorities



OIR 2017 Priorities

- Quality Management
- CLIA Waiver
- EAP
- Patient outreach

21st Century Cures

Susceptibility test interpretive criteria for microorganisms (Section 3044)

Risk-Based Framework for LDTs

The FDA believes that patients and health care providers need accurate, reliable, and clinically valid tests to make good health care decisions - inaccurate or false test results can harm individual patients. We have been working to develop a new oversight policy for laboratory developed tests, one that balances patient protection with continued access and innovation, and realize just how important it is that we continue to work with stakeholders, our new Administration, and Congress to get our approach right. We plan to outline our view of an appropriate risk-based approach in the near future. It is our hope that such an approach will help guide continued discussions.

Parallel Review with CMS

- Pilot program began in 2011
  - FDA, CMS, and sponsor meet (via Pre-Submission) to discuss proposed pivotal clinical trial design
  - FDA and CMS simultaneously review clinical data for PMA approval and national coverage determination
- Examples in OIR:
  - Exact Science's Cologuard stool-based screening for colorectal cancer
  - Foundation Medicine's FoundationOne comprehensive genetic profiling assay incorporating multiple companion diagnostics to support precision medicine in oncology
- To be considered for program, send request to:

  Parallel-Review@fda.hhs.gov

Payer Participation in Pre-Submissions

- New! Sponsors who are not interested/eligible for parallel review can still obtain CMS or private payer feedback in their Pre-Submission meetings
- Private payers with expressed interest:
  - BCBS
  - Duke Evidence Synthesis Group
  - ECRI
  - Humana
  - Kaiser
  - National Institute for Health and Care Excellence
  - SelectHealth/Intermountain Health
- To request payer participation in your Pre-Submission, contact: CDRHPayerCommunications@fda.hhs.gov

Expedited Access Pathway (EAP)

- Voluntary program for medical devices that demonstrate a credible potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions.
- Goal: ***help patients have more timely access to these medical devices by expediting their development, assessment, and review, while preserving our statutory standards for safety and effectiveness and protecting patients***
- Described in EAP Guidance (final April 2015)

EAP Update

- 3 EAP designation requests granted by OIR to date.

Highlights of Program Improvements

- Revamped or created >20 tools and templates for reviewers, provided training to staff
- Published Data Development Plan (DDP) examples to FDA website: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm441467.htm

Lessons Learned

- When to Submit EAP Designation
  - Ability to demonstrate technical and clinical success
- Appropriate level of detail in Data Development Plan (DDP)
  - Striking the balance
- Key placeholders in Data Development Plan
  - Use of “TBD”

SaMD Clinical Evaluation Draft Guidance (N41) addresses key cross-cutting issues

- When may clinical data be needed for SaMD and SaMD modifications?
- How should evidence be generated?
- What level of evidence is appropriate?

SaMD Evaluation Framework is based on four independent factors

- Novel vs. Not Novel
- Diagnostic vs. Not Diagnostic
- State of Healthcare situation or condition (3 levels)
- Significance of information provided by SaMD to healthcare decision (3 factors)

2 levels x 2 levels x 3 levels x 3 factors = 36 possible combinations that are then combined into 4 broad SaMD categories

Deciding When to Submit a 510(k) for a Change to an Existing Device

Draft Guidance for Industry and FDA Staff

- No paradigm change from original guidance issued in 1997
- Changes made for clarity, including interpretation of key terms such as "could significantly affect"
- Describes a logic scheme for determining when a 510(k) is required
- Flowcharts matched with text for ease of use
- More examples
- Recommendations on documentation

Scope includes legally marketed devices subject to 510(k) requirements

- Excludes PMA devices and 510(k)-exempt devices
- Does not apply to software-specific changes - Separate software guidance
- Does apply to non-software changes to software devices or devices containing software (e.g., labeling)

Research Use Only IVD Products

Safety Communication

- Exempt from most regulatory controls, including:
  - Premarket review to assure performance characteristics are proven
  - Quality System to ensure consistent manufacturing of the finished product

- Should not be distributed for clinical diagnostic purposes
  - Should be labeled RUO
  - Should NOT be marketed for clinical use, such as through statements in labeling, advertising, or promotion regarding performance claims, instructions for clinical interpretation, clinical information, or other information that suggests the product may be for clinical diagnostic use

Precision Medicine

Many advances in precision medicine will depend on the safe and effective use of next generation sequencing (NGS) technology. As part of the Precision Medicine Initiative (PMI), FDA has been focused on optimizing FDA's regulatory oversight for NGS in vitro diagnostic (IVD) tests to help accelerate research and the clinical adoption of precision medicine while assuring the safety and effectiveness of these tests.

Precision Medicine Draft Guidances

- “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics” - Draft Guidance
- “Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases” - Draft Guidance

Recent Draft Guidances

- 510(k) Third Party Review Program*
- Deciding When to Submit a 510(k) for a Change to an Existing Device*
- Deciding When to Submit a 510(k) for a Software Change to an Existing Device*
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*
- Unique Device Identification System: Form and Content of the Unique Device Identifier (UDI)*
- Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies
- Emergency Use Authorization of Medical Products and Related Authorities

*Docket currently open for comments

Recent Final Guidances

- Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
- Patient Preference Information
- General Wellness: Policy for Low Risk Devices
- Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices

510(k) Third Party Premarket Review Program Enhancements

1. **Give 3Ps the tools they need to succeed**
   a. Enhanced training (similar to RCP)
   b. Redacted review memos (already have decision summaries for IVDs)
   c. Additional device-specific guidance
   d. Keep 3Ps up-to-date on policy changes
   e. Provide updated decision memo templates for use by 3Ps
2. **Monitor quality of 3P reviews**
   a. Review staff surveys
   b. General audits of 3P review memos
   c. Audits of 3P adherence to device-specific guidance
3. **Address poor performers**
   a. Finalize draft guidance on accreditation, reaccreditation, suspension and withdrawal
   b. Audits of accreditation
   c. Publish performance on website

IVD PMA Approvals

- Medtronic MiniMed 670G hybrid closed loop system
  - ***First-in-the-world approval of an "artificial pancreas"***
  - Intended to automatically monitor glucose (sugar) and provide appropriate basal insulin doses in people 14 years of age and older with type 1 diabetes
  - Will provide greater freedom and improve the quality of life for patients with type 1 diabetes

- Roche Molecular, Cobas EGFR Mutation Test v2
  - ***First "liquid biopsy test" approved for use by FDA***
  - A blood-based companion diagnostic for the cancer drug Tarceva (erlotinib)

IVD PMA Approvals Cont.

- Medtronic MiniMed, 630G System with SmartGuard™
  - Can temporarily suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value
- Medtronic MiniMed, iPro2 Continuous Glucose Monitoring (CGM) System
  - A professional-use Continuous Glucose Monitoring (CGM) System that measures glucose levels in fluid under the skin for up to six days
- Roche molecular HPV assay with SurePath sample
  - ***First HPV test approved for use with SurePath sample medium***

De Novo Classifications

- Clever Culture Systems, Agar Plate Assessment System (APAS) Compact
  - Automates urine culture plate imaging and interpretation as an aid in the diagnosis of urinary tract infection
- Asuragen, inc., Quantidex Qpcr Bcr-Abl Is kit
  - First nucleic acid-based quantitation test for use during treatment of chronic myeloid leukemia (CML) patients
- KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay
  - Aids in the diagnosis of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD)
  - These disorders are often misdiagnosed as multiple sclerosis (MS) but require a different treatment

Notable 510(k) Clearances

- Liofilchem, MIC test strips for ceftolozane/tazobactam
  - A new AST device that provides susceptibility/resistance results for a newly approved drug that specifically targets multi-drug resistant pathogens
- Cepheid, Xpert Carba-R Assay
  - First test to detect specific genetic markers for Carbapenem-resistant Enterobacteriaceae (CRE) directly from clinical specimens
  - Will allow hospitals to more quickly identify dangerous bacteria resistant to certain antibiotics
- Vermillion OVA1 NG
  - Intended to help assess the likelihood a malignancy is present in patients with an ovarian adnexal mass for which surgery is planned
  - A qualitative serum test that combines the results of five immunoassays into a single numeric result

Dual 510(k) and CLIA Waivers by Application

- BioFire Diagnostics, FilmArray Respiratory Panel EZ (RP EZ) on the FilmArray 2.0 EZ
  - Novel CLIA Waiver for a multiplexed nucleic acid test for multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs

- Roche Molecular (Iquum), cobas Liat Influenza A/B & RSV Assay on the cobas Liat System
  - Real-time PCR test that differentiates flu and RSV

CLIA Waivers by Application

- YD Diagnostics Corp., URiSCAN Optima Chemistry Test System
  - A semiquantitative urine analyzer and test strips for the measurement of Albumin, Creatinine, and ACR (Albumin Creatinine Ratio)
- Princeton BioMeditech Corporation, BioSign Flu A+B
- Guangzhou Wondfo Biotech Co., Wondfo One Step Strep A Swab Test

Approval of CLIA Waivers for Modified Test Systems Previously Waived by Application:

- Orgenics, Alere Determine™ HIV-1/2 Ag/Ab Combo
- Princeton BioMeditech StatusFirst Strep A

Zika Emergency Use Authorizations

- Vela Diagnostics USA, Inc.'s Sentosa® SA ZIKV RT-PCR Test
- Roche Molecular Systems, Inc.'s LightMix® Zika rRT-PCR Test
- InBios International, Inc.'s ("InBios"), ZIKV Detect™ IgM Capture ELISA
- Luminex Corporation's xMAP® MultiFLEX™ Zika RNA Assay
- Siemens Healthcare Diagnostics Inc.'s VERSANT® Zika RNA 1.0 Assay (kPCR) Kit
- Viracor-IBT Laboratories, Inc.'s ("Viracor-IBT") Zika Virus Real-time RT-PCR test
- Hologic, Inc.'s Aptima® Zika Virus assay
- altona Diagnostics RealStar® Zika Virus RT-PCR Kit
- ARUP Laboratories Zika Virus Detection by RT-PCR
- Focus Diangositcs, Inc’s Zika Virus RNA Qualitative RT-PCR
- CDC’s Trioplex rRT-PCR
- CDC’s Zika MAC-ELISA

Resources for Zika Test Developers

- Draft EUA review templates for Zika
  - Serological IgM Draft EUA Review Template
  - Molecular Draft EUA Review Template
- Zika Virus Reference Materials for Nucleic acid (NAT)-based IVDs

Send requests to: CDRH-ZIKA-Templates@fda.hhs.gov