FDA UPDATE

Elizabeth Hillebrenner, MSE
Food and Drug Administration
Office of *In Vitro* Diagnostics and Radiological Health (OIR)

October 13, 2016
AMDM 2016 IVD Focus Meeting
Los Gatos, CA

SUMMARY

1. CDRH Vision & Strategic Priorities
2. Payer Communications Task Force
3. General Guidance Documents
4. MDUFA IV: Tentative Agreement
5. Precision Medicine Initiative (PMI)
6. Research Use Only (RUO) IVD Products
7. IVD Specific Guidance Documents, Workshops, & Panel Meetings
8. Approvals, Classifications, Clearances, & Authorizations

1.

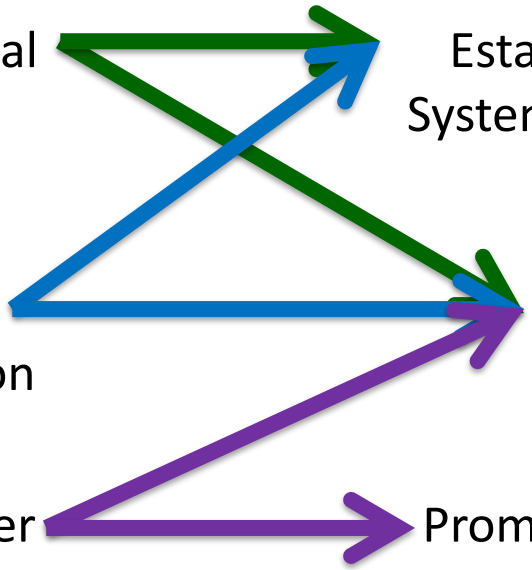
CDRH VISION & STRATEGIC PRIORITIES

CDRH 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

2014-2015	2016-2017
Strengthen the Clinical Trial Enterprise	Establish a National Evaluation System for Medical Devices (NEST)
Strike the Right Balance Between Premarket and Postmarket Data Collection	Partner with Patients
Provide Excellent Customer Service	Promote a Culture of Quality and Organizational Excellence



2.

PAYER COMMUNICATIONS TASK FORCE

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

3.

GENERAL GUIDANCE DOCUMENTS

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

4.

MDUFA IV: TENTATIVE AGREEMENT

Medical Device User Fee Act 4: Tentative Agreement

- Agreement in principle among FDA, AdvaMed, MDMA, MITA, ACLA
- Establish a dedicated premarket Quality Management team
- Conduct an Independent Assessment of M3 and M4
- Improve:
  - Consistency through enhanced supervisory oversight and routine quality audits
  - Quality and consistency of Additional Information and Major Deficiency letters
  - Third Party Review Program
  - Tracking and reporting of performance commitments;
  - Time reporting – complete time reporting by end of FY2022
  - Recruitment and retention of FDA employees through a more effective strategy and incentive pay

Medical Device User Fee Act 4: Tentative Agreement

- Improved Performance:
  - Reduce average total time to decision to 108 days for 510(k)s and to 290 days for PMAs by the end of FY2022
  - Ramp up to completion of 70% of De Novo submissions within 150 days by the end of FY2022
  - Ramp up to providing written feedback on at least 1,950 Pre-Submissions within 70 days or 5 calendar days prior to the scheduled meeting, whichever comes sooner, by the end of FY2022
  - FDA will improve the CLIA waiver by application process
- Enhance IT infrastructure to collect and report on structured data, allow sponsors to view individual submission status in near real-time, and develop structured electronic submission templates as a tool to guide Industry's preparation of premarket submissions

Medical Device User Fee Act 4: Tentative Agreement

- New Efforts:
  - Digital Health: Improve consistency in review of software, streamline and align FDA review processes with software lifecycles
  - Patient Engagement: Develop internal expertise to support the increased use of patient preference information and patient reported outcomes in premarket submissions
  - Real-World Evidence: Enhance internal expertise and support establishment and pilots conducted by NEST Coordinating Center to enable greater use of RWE in the premarket setting
  - Seek authority to establish a conformance assessment program for certified testing laboratories that evaluate medical devices according to certain FDA-recognized standards
- Seek authority to permit FDA to keep over-collections and eliminate 5th year offset
- Treat laboratory developed tests no less favorably than other device subject to MDUFA performance goals and report on performance
- Total MDUFA fee revenue target of $999.5 million over 5 years, to be adjusted for inflation

MDUFA IV Performance Goals

Submission Type	Action	FDA Review Days	Percent of Submissions to Meet FDA Days				
			FY18	FY19	FY20	FY21	FY22
510(k)s	Substantive Interaction	60	95%	95%	95%	95%	95%
	Decision	90	95%	95%	95%	95%	95%
De Novos	Decision	150	50%	55%	60%	65%	70%
Original PMAs & Panel Track Supplements	Substantive Interaction	90	95%	95%	95%	95%	95%
	Decision if No Panel	180	90%	90%	90%	90%	90%
	Decision With Panel	320	90%	90%	90%	90%	90%
	Decision following Panel	60	*As resources permit*				
	Response to Approvable	60	*As resources permit*				
180 Day PMA Supplements	Substantive Interaction	90	95%	95%	95%	95%	95%
	Decision	180	95%	95%	95%	95%	95%
Real Time Supplements	Decision	90	95%	95%	95%	95%	95%
Pre-Submissions	Written Feedback	70 or 5d prior to mtg	1,530 (65%)	1,645 (70%)	1,765 (75%)	1,880 (80%)	1,950 (83%)
CLIA Waiver by Applications	Substantive Interaction	90	90%	90%	90%	90%	90%
	Dual CLIA/ 510(k)	180	90%	90%	90%	90%	90%
	Decision if No Panel	150	90%	90%	90%	90%	90%
	Decision With Panel	320	90%	90%	90%	90%	90%

Workshops & Conferences (Medical Devices)

2016 Medical Device Meetings and Workshops

2015 Medical Device Meetings and Workshops

Medical Device Webinars and Stakeholder Calls

Public Meeting - Medical Device User Fee Amendments, November 2, 2016

The Food and Drug Administration (FDA) is announcing a public meeting entitled "Medical Device User Fee Amendments."

The purpose of the meeting is to discuss proposed recommendations for the reauthorization of the Medical Device User Fee Amendments (MDUFA) for fiscal years (FYs) 2018 through 2022. MDUFA authorizes FDA to collect fees and use them for the process for the review of medical device applications. The current legislative authority for MDUFA expires October 1, 2017. At that time, new legislation will be required for FDA to continue collecting medical device4 user fees in future fiscal years. Following discussions with the device industry and periodic consultations with public stakeholders, the Federal Food, Drug, and Cosmetic Act (the FD&C Act) directs FDA to publish the draft recommendations for the reauthorized program in the Federal Register, hold a meeting at which the public may present its views on such draft recommendations, and provide for a period of 30 days for the public to submit written comments on such draft recommendations. FDA will then consider such public views and comments and revise such recommendations as necessary.

Date, Time and Location

This meeting will be held Wednesday, November 2, 2016, from 9:00 a.m. – 5:00 p.m. at the following location:

FDA White Oak Campus
10903 New Hampshire Avenue
Bldg. 31, Room 1503 (the Great Room)
Silver Spring, MD. 20993

5.

THE PRECISION MEDICINE INITIATIVE (PMI)

The Precision Medicine Initiative (PMI)

To enable a new era of medicine through research and technology that empowers patients, researchers, and providers to work together toward development of individualized treatments.

Precision Medicine

- Flexible, streamlined, voluntary, collaborative approach with the clinical community using crowdsourcing, expert forums, and levels of evidence for next-generation sequencing (NGS) for germline diseases
- Scalable to other NGS and other tests
- Conformity with consensus standards developed by the clinical community to support analytical validity
- Evidence generated from and interpreted by FDA-recognized, public databases to support clinical validity

Precision Medicine: Recent Actions

- Draft Guidances
  - Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics
  - Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases
- Public Workshop
  - Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests - September 23, 2016
- precisionFDA

6.

RESEARCH USE ONLY (RUO) IVD PRODUCTS

Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only

Guidance for Industry and Food and Drug Administration Staff

Document issued on: November 25, 2013

The draft of this document was issued on June 1, 2011.

For questions regarding this document contact Elizabeth Mansfield, by phone at (301) 796-4664, or by email at elizabeth.mansfield@fda.hhs.gov. For questions relating to devices regulated by CBER, contact the Office of Communications, Outreach and Development, CBER at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Biologics Evaluation and Research

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM376118.pdf

RUO IVD Products

- 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

Safety Alerts for Human Medical Products

2016 Safety Alerts for Human Medical Products

2015 Safety Alerts for Human Medical Products

2014 Safety Alerts for Human Medical Products

2013 Safety Alerts for Human Medical Products

2012 Safety Alerts for Human Medical Products

Mass Spectrometers by Sciex: Safety Communication - Incorrect Assignment of Test Results

Including:

Sciex API 3200 LC/MS/MS System, 3200MD QTRAP LC/MS/MS System, Triple Quad 4500 LC/MS/MS System, and the QTRAP 4500 LC/MS/MS equipped with:

- the Analyst Software Versions 1.6.1 and 1.6.2, and
- the MultiQuant Software Versions 3.0, 3.0.1, and 3.0.2.

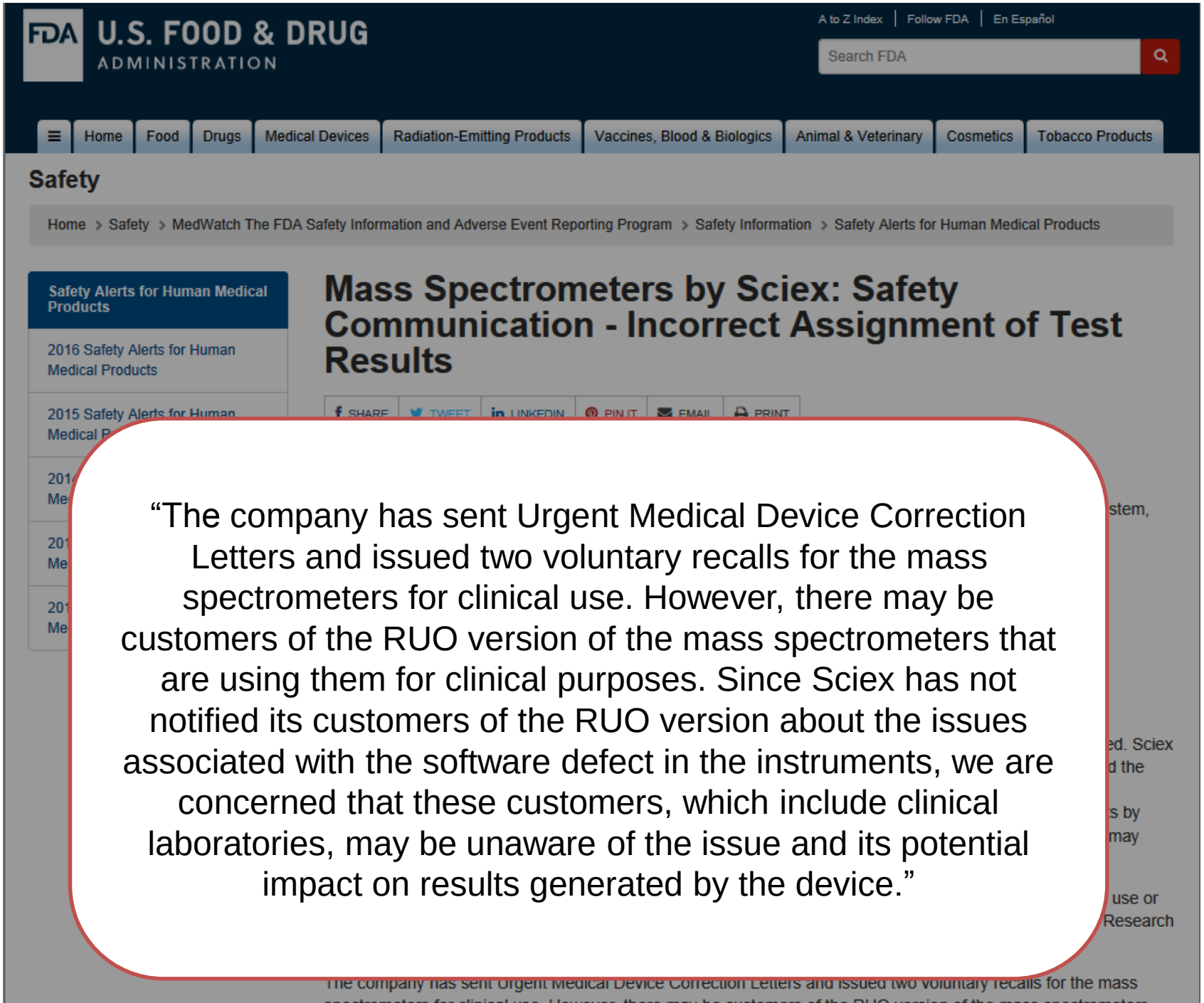
[Posted 09/01/2016]

AUDIENCE: Risk Manager, Laboratory

ISSUE: The FDA is alerting lab staff and health care professionals about a software defect in Sciex mass spectrometers. This software defect may cause the devices to incorrectly assign results to samples analyzed. Sciex notified the FDA that, under certain conditions, the defect in the software versions identified above may lead the devices to display results that do not match the specimens tested. This is of concern because health care professionals may make inaccurate clinical diagnoses or inaccurate medical treatment decisions for patients by relying on incorrect results from the devices. A potential inaccurate clinical diagnosis or treatment decision may lead patients to experience serious adverse health consequences.

The mass spectrometers manufactured by Sciex are medical devices specified either for clinical diagnostic use or for research use only (RUO). RUO devices are typically in a development stage and must be labeled "For Research Use Only. Not for use in diagnostic procedures."

The company has sent Urgent Medical Device Correction Letters and issued two voluntary recalls for the mass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Mass Spectrometers by Sciex: Safety Communication - Incorrect Assignment of Test Results
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“The company has sent Urgent Medical Device Correction Letters and issued two voluntary recalls for the mass spectrometers for clinical use. However, there may be customers of the RUO version of the mass spectrometers that are using them for clinical purposes. Since Sciex has not notified its customers of the RUO version about the issues associated with the software defect in the instruments, we are concerned that these customers, which include clinical laboratories, may be unaware of the issue and its potential impact on results generated by the device.”

7.

IVD GUIDANCES, WORKSHOPS, AND PANEL MEETINGS

IVD Specific Guidances

- Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use
- Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use
- Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices
- Radiation Biodosimetry Medical Countermeasure Devices
- Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product (DRAFT)

Workshops

- Public Workshop - Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests - September 23, 2016
- Public Workshop - Liquid Biopsies in Oncology Drug and Device Development, An FDA-AACR public workshop, July 19, 2016
- Workshop - 9th Annual Medical Device and Diagnostics Statistical Issues, Co-Sponsored by AdvaMed and FDA, May 3-4, 2016
- Public Workshop - Mass Spectrometry in the Clinic: Regulatory Considerations Surrounding Validation of Liquid Chromatography-Mass Spectrometry Based Devices, May 2, 2016

Advisory Committee Panel Meetings

- Microbiology Devices Panel
  - August 16, 2016: Over-the-counter (OTC) diagnostic tests for the detection of pathogens causing infectious diseases, focusing on respiratory and sexually transmitted infections (STI)

- Clinical Chemistry and Clinical Toxicology Devices Panels
  - August 10, 2016: De novo request for the SEEKER Newborn Screening System (SEEKER System), by Baebies, Inc
  - July 22, 2016: 510(k) submission for the Alere Afinion™ HbA1c Dx point-of-care test system
  - July 21, 2016: PMA panel-track supplement for Dexcom, Inc.'s, Dexcom G5® Mobile Continuous Glucose Monitoring System (CGM) device

8.

APPROVALS, CLASSIFICATIONS, CLEARANCES, & AUTHORIZATIONS

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
  - A qualitative serum test that combines the results of five immunoassays into a single numeric result
  - Intended to help assess the likelihood a malignancy is present in patients with an ovarian adnexal mass for which surgery is planned

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)
- 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

Median Review Time: 5 days

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


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