FDA Update: Office of In Vitro Diagnostics

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Director, Office of In Vitro Diagnostics
(OIVD/OHT7)

FDA-Industry IVD Roundtable

May 22, 2023

OHT7: Office of In Vitro Diagnostics

Office Director: **Timothy Stenzel**
Deputy Office Directors: **Toby Lowe** (Acting), **Brittany Schuck,** Vacant
Associate Director for Regulatory Programs: **[Toby Lowe]**
Associate Director Strategic Initiatives: Vacant
Chief Medical Officer & Associate Director for Medical Affairs: **Sara Brenner**
Associate Director for Professional Development: Vacant
Associate Director for Operations: **Jennifer Draper** (Acting)
OIVD Immediate Office Staff:
Stacey Borenstein, Mrigendra Bastola, Jennifer Campbell, Keith Eugene Campbell, Victoria Derbyshire, Daniel Edelman, Abdi Hashir, Dina Jerebitski, Marina Kondratovich, Stephanie Krmenec, Kristofor Langlais, Ryan Lubert, Jules Nchoutmboube, Mckenna Tennant, Grace Tran, Thierry Vilboux, [Amy Zale]

Division of Immunology and Hematology Devices (DIHD)

Division Director **– Lea Carrington**
Deputy Division Director **– Takeesha Taylor-Bell**

Division of Chemistry and Toxicology Devices (DCTD)

Division Director **– Marianela Perez-Torres** (Acting)
Deputy Division Director **– Paula Caposino** (Acting)

Division of Molecular Genetics and Pathology (DMGP)

Division Director **– Donna Roscoe** (Acting)
Deputy Division Director **– Donna Roscoe**

Division of Microbiology Devices (DMD)

Division Director **– Uwe Scherf**
Deputy Division Director **– Kristian Roth**

Division of Program Operations and Management (DPOM)

Division Director **– Amy Zale** (Acting)
Deputy Division Director – Vacant

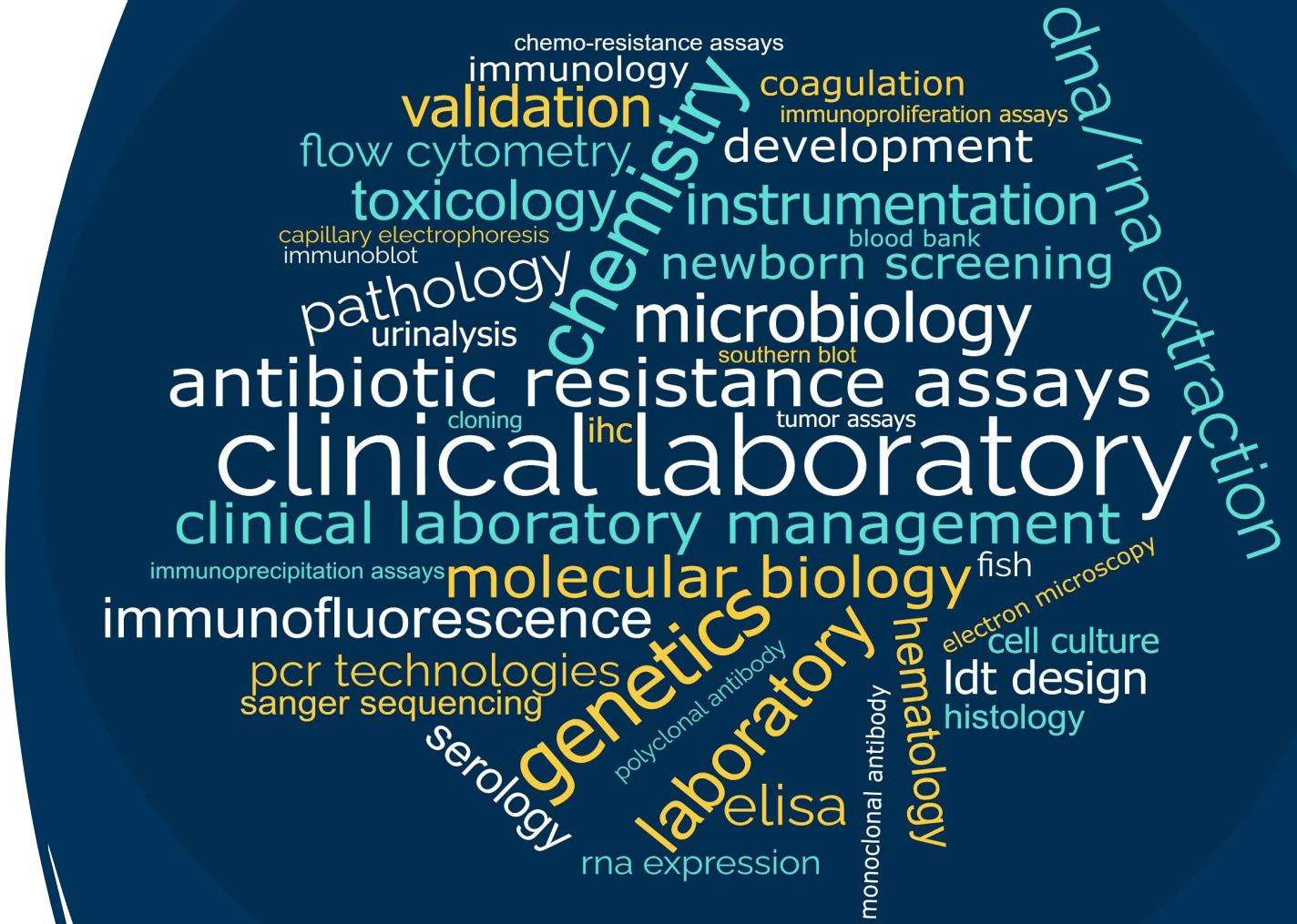
OHT7 Staff Have a Wealth of Experience

over 300 highly motivated staff

widespread experience

various specialties

>96% customer satisfaction rating in 2022



OHT7: Key Activities

- Stakeholder Outreach and Engagement
- Pre-submissions and Breakthrough Designation Requests
- Emergency Use Authorizations (EUAs)
- Marketing Submission Reviews
  - 510(k) Premarket Notifications
  - De Novo Requests
  - Premarket Approval (PMA) applications
- CLIA Complexity Determinations and Waiver by Application Reviews
- Investigational Device Exemptions (IDEs)
- Guidance Document Development
- Postmarket Surveillance
- Compliance and Enforcement Activities

2022 Was a Busy Year!

Premarket Review:

~ 1500 Submissions

- ~90 PMAs and PMA Supplements
- ~250 510(k)s
- ~20 De Novos
- ~550 Pre-Submissions
- ~60 IDEs
- 1 CLIA Waiver by Application
- 9 Dual 510(k) and CLIA Waiver by Application
- ~500 EUAs

Surveillance:

~1,200,000 Medical Device Reports (MDRs)

- ~800,000 initial MDRs
- ~400,000 supplemental MDRs

Office Highlights for 2022

- First de novo authorization for a newborn screening test for Spinal Muscular Atrophy
- First companion diagnostic for HER2-low Breast Cancer, to identify breast cancer patients belonging to the new classification of HER2-low who are now eligible for targeted treatment
- Clearance of Tidepool Loop, which created a pathway to market for stand-alone automated insulin dosing systems and paving the way for smaller developers to reach the market
- Removal of contraindication for several Continuous Glucose Monitoring systems for use during pregnancy
- First in vitro diagnostic test for early detection of amyloid plaques associated with Alzheimer's disease
- First commercially available laboratory-based blood test to evaluate concussions
- First point-of-care diagnostic test for pulmonary anthrax, as an aid in the diagnosis of inhalation anthrax
- First multiplex test for bacterial and yeast detection in synovial fluid to aid in the diagnosis of bone and joint infections (BJI)
- Multiple breakthrough designations

Office Highlights 2022 - Continued

- COVID-19 EUA Summary since May 2022
  - Total of 1050 COVID EUAs closed
  - 145 test authorizations

- Mpox Summary since September 7, 2022
  - ~200 Mpox-related files closed
    - 165 pre-EUA/Intent to submit EUA submissions
    - 31 EUAs – 8 Authorized NAATs, including Automated, POC, ITAP collaboration
    - 4 510(k)s cleared, expanding access to CDC NVO test

Updates on Annual Influenza Reactivity Panel

- The CBER Human Influenza Virus Panel (2023) is now available to manufacturers of FDA cleared influenza antigen detection tests.

- The panel can be requested by email: CBERInfluenzaPanelRequests@fda.hhs.gov

- By regulation 21 CFR 866.3328, annual reactivity testing must be performed with contemporary influenza strains. This panel is the source for appropriate 2023 strains.

- Manufacturers of FDA cleared molecular influenza tests may also obtain the panel based on availability at the time of the request.

COVID-19 IVD EUAs Authorized as of May 18, 2023

302

Molecular diagnostic tests

- 34 Pooling
- 69 Asymptomatic single use screening
- 7 Serial screening
- 27 Multi-analyte (i.e., SARS-CoV-2 + Influenza)
- 23 Point-of-care
- 78 Home collection
  - 16 Direct-to-consumer
  - 6 Multi-analyte
  - 15 Saliva home collection
- 21 Standalone home collection kits
- 3 Standalone saliva collection devices
- 1 Prescription at-home test
- 4 Over-the-counter (OTC) at-home tests

63

Antigen diagnostic tests

- 57 Point-of-care
- 2 Prescription at-home tests
- 31 Over-the-counter (OTC) at-home tests
- 48 Serial Screening
- 3 Serial Testing
- 3 Multi-Analyte

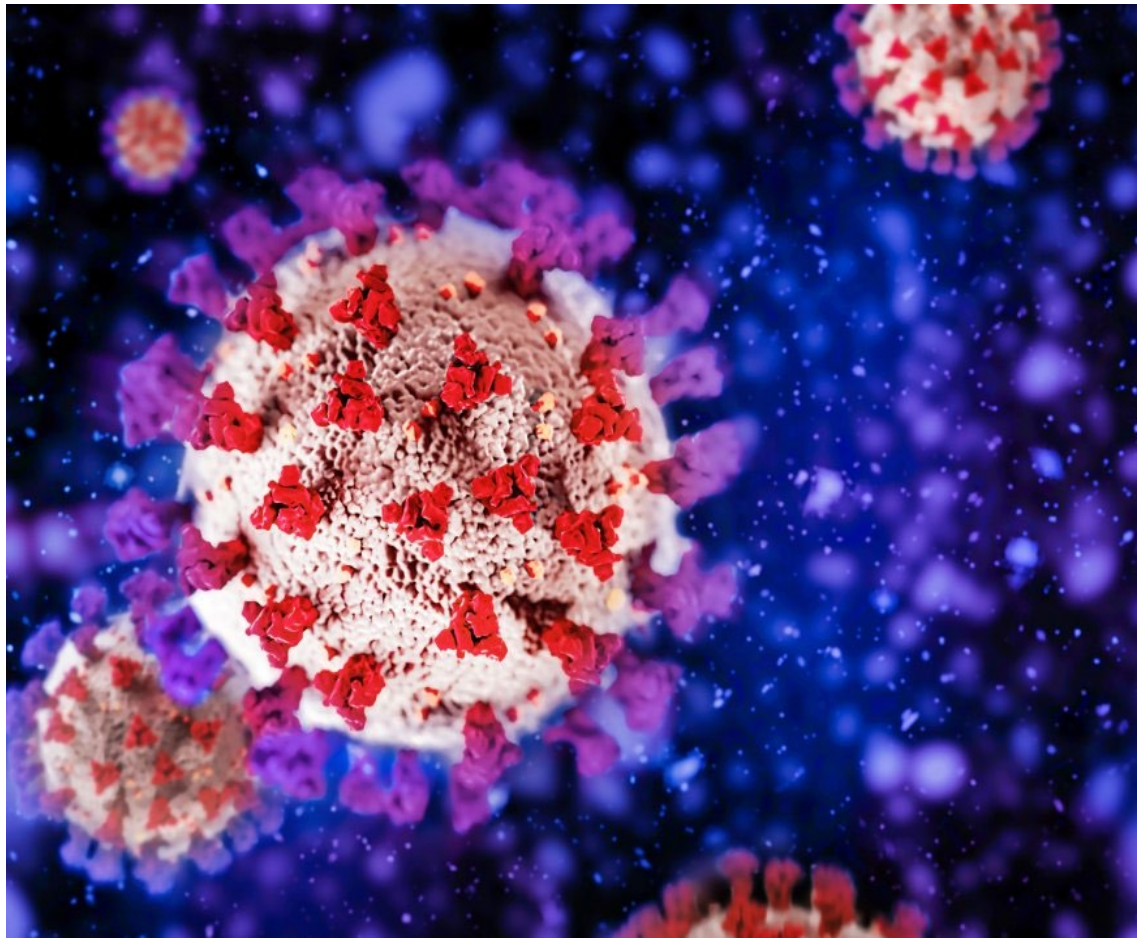
83

Serology and other immune response tests

- 13 Point-of-care
- 3 Neutralizing antibody tests
- 16 Semi-quantitative
- 1 Quantitative
- 1 Home collection

In Vitro Diagnostics EUAs: Novel Tests for SARS-CoV-2

- **InspectIR COVID-19 Breathalyzer**: First COVID-19 diagnostic test using breath samples. Authorized April 14, 2022
- **Labcorp VirSeq SARS-CoV-2 NGS Test**: First genotyping test for SARS-CoV-2. Authorized June 10, 2022
- **Twist Bioscience SARS-CoV-2 NGS Assay:** Test for genotyping and identifying specific mutations of SARS-CoV-2. Authorized July 28, 2022



Independent Test Assessment Program (ITAP) provides support for FDA authorization of rapid at-home COVID-19 tests

The National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx) initiative has established the Independent Test Assessment Program (ITAP) in order to accelerate regulatory review and availability of high-quality, accurate, and reliable over-the-counter COVID-19 tests to the public.

Tests with Emergency Use Authorization (EUA) after being evaluated through ITAP

- Azure Biotech, Inc.
- SD Biosensor distributed by Roche
- Siemens
- Maxim Biomedical
- Osang, LLC
- Princeton Biomeditech Corp.
- ANP Technologies, Inc
- Xiamen Boson Biotech Co., Ltd
- Watmind
- Genbody
- Lucira
- Mologic
- PHASE Scientific International, Ltd.

- This program is incredibly beneficial to increasing access to rapid tests by quickly and consistently gathering the critical data companies need to request EUA and subsequently enter the U.S. market once authorized.
- These tests contribute significant manufacturing volume for OTC COVID-19 tests on the US market

At-Home OTC COVID-19 Diagnostic Tests

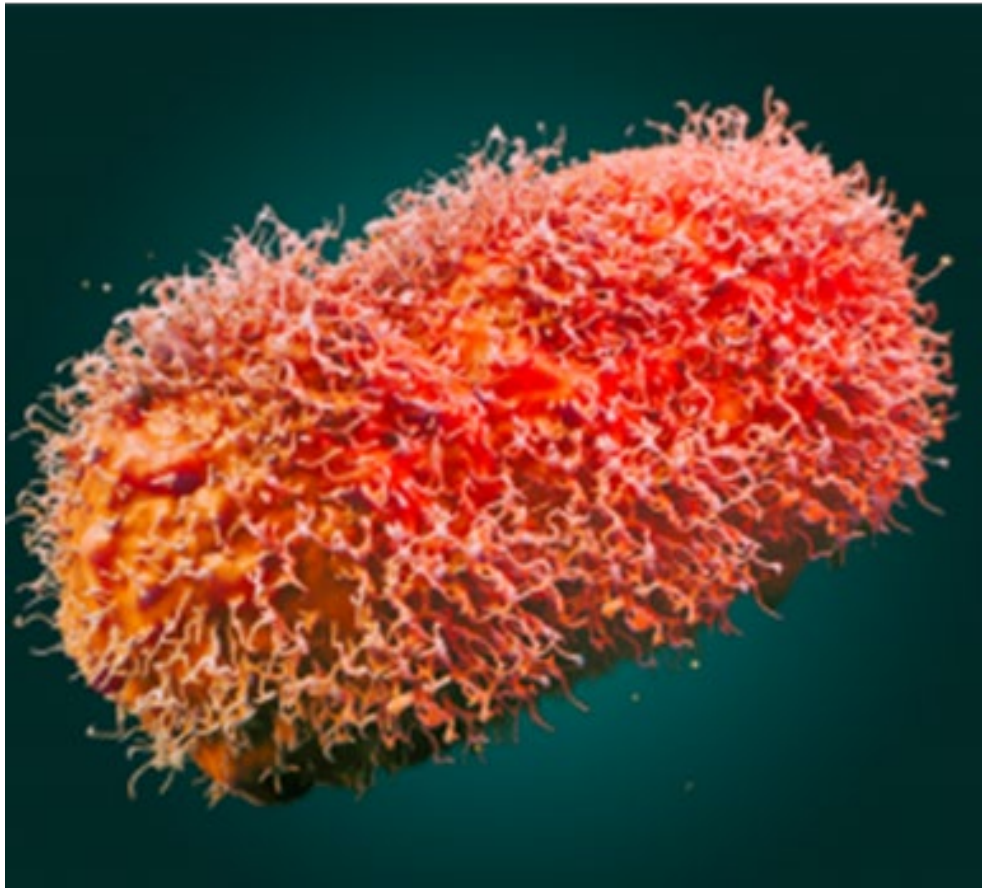
- Over 30 OTC COVID-19 diagnostic tests authorized
- FDA web page provides List of Authorized At-Home OTC COVID-19 Diagnostic Tests including links to home use instructions for each test
- FDA Safety Communication regarding repeat testing for at-home COVID-19 antigen tests (updated November 17, 2022):
  - *Perform repeat, or serial testing following a negative result on any at-home COVID-19 antigen test,* ***whether or not you have symptoms***

FDA Authorizes First Over-the-Counter At-Home Test to Detect Both Influenza and COVID-19 Viruses

- **Lucira COVID-19 & Flu Home Test:** First over-the-counter (OTC) diagnostic test for detection and differentiation of influenza A and B, and SARS-CoV-2. Authorized February 24, 2023
- At-home test kit provides results from self-collected nasal swab samples in roughly 30 minutes
- Authorization underscores the Agency's continued commitment to increase availability of accurate and reliable at-home diagnostic tests

FDA has taken the following steps to support the response to the mpox outbreak:

- Engaged with CDC and other agencies to enable use of CDC's FDA cleared Non-Variola Orthopox screening assay, which can detect Monkeypox from a lesion sample, in 65 CDC Laboratory Response Network (LRN) labs, as well as CDC-designated labs outside the LRN
- Cleared use of additional reagents, extraction platforms and automation to expand testing capacity
- Issued a guidance, Policy for Monkeypox [mpox] Tests to Address the Public Health Emergency that describes review priorities for Emergency Use Authorization
- Exercised enforcement discretion for laboratory developed tests (LDTs) available for *orthopoxvirus*, or specifically for the monkeypox virus
- Issued FDA Safety Communication: For Monkeypox testing, use lesion swab samples to avoid false results



CDRH's Efforts to Return to Normal

- Reauthorization of the Medical Device User Fee Amendments (MDUFA) authorizes FDA to collect user fees for the review of device applications for fiscal years 2023 through 2027
- CDRH is accepting and immediately initiating the review process for all new in vitro diagnostic (IVD) premarket submissions and pre-submissions in accordance with the performance goals established in the MDUFA V Commitment Letter
- OHT7 is diligently working to clear the backlog of premarket submissions received during MDUFA IV, which are being reviewed under extended timelines due to prioritization of work to support the COVID-19 PHE

FDA Encourages Developers to Seek Traditional Premarket Review for Most COVID-19 Test Types

September 28, 2022 – Guidance Update

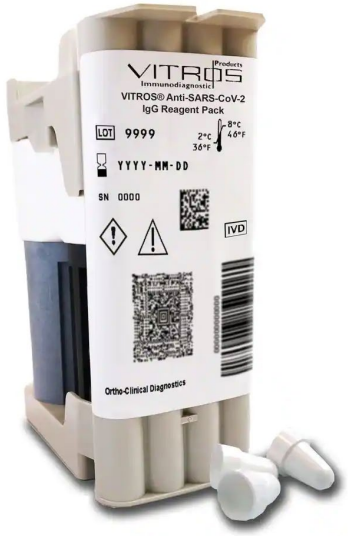
- FDA generally expects EUAs (or marketing authorization) for all COVID-19 tests
- Encourage traditional review pathways
- Reduced types of tests prioritized for review under EUA

January 12, 2023 – Guidance Update

- Revised the duration for which the policies in the guidance are intended to remain in effect
- Policies in the guidance are intended to remain in effect only for the duration of the declaration under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by the Secretary of Health and Human Services (HHS) on February 4, 2020, declaring that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the novel coronavirus (2019-nCoV).

*This slide presents high level discussion points. Please refer to the guidance document for the details and official policies.

The 510(k) Pathway is Available for COVID-19 Molecular, Antigen, and Serology Tests



Marketing authorization using the De Novo review pathway, a regulatory pathway for low- to moderate-risk devices of a new type has been granted for the following:

BioFire Respiratory Panel 2.1 (RP2.1): First COVID-19 molecular diagnostic test. Granted March 17, 2021

Quidel Sofia 2 SARS Antigen+ FIA: First COVID-19 antigen test. Granted March 8, 2023

VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Test and Anti-SARS-CoV-2 IgG Test: First COVID-19 serology tests. Granted May 5, 2023

- In addition to these De Novos, FDA has also cleared additional COVID-19 tests using the 510(k) pathway.
- We welcome additional COVID-19 test submissions through the traditional review pathways.

Final COVID-19 Transition Guidances

- On March 27, 2023, CDRH issued two guidance documents to assist with transition plans for medical devices that were issued EUAs or fall within certain enforcement policies issued to support the response to the COVID-19 pandemic
  - Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19)
    - Referred to as "EUA Transition Guidance"
  - Transition Plan for Medical Devices That Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
    - Referred to as "Enforcement Policies Transition Guidance"
    - FDA's Policy for Coronavirus Disease-2019 Tests (Revised) and Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests (Revised) are outside scope

*This slide presents high level discussion points. Please refer to the guidance documents for the details and official policies.

COVID-19 Transition Highlights

PHE and EUA Declarations

- The Public Health Emergency declared under Section 319 of the Public Health Service Act ended on May 11, 2023.
- The determination and declarations under Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) remain in effect.
  - For each EUA declaration, FDA will publish advance notice of termination in the Federal Register, **180 days** before termination of the EUA declaration and associated EUAs.

COVID-19 Transition Guidances

- Outline the FDA's general recommendations to transition from certain policies adopted and operations implemented during the COVID-19 pandemic to normal operations, including the FDA's recommendations for:
  - Developing a transition implementation plan for in vitro diagnostics (IVDs) with an EUA,
  - Submitting an IVD marketing submission,
  - Taking other actions with respect to these IVDs, and
  - Additional information related to test developers and COVID-19 tests.

Transition Period

DEVICE MARKETED UNDER	IMPLEMENTATION START (Day 0)	TRANSITION (Days 1-179)	PREMARKET SUBMISSION DUE (Day 180)
EUA	FR publication of Advance Notice of Termination for each EUA declaration termination	Continue marketing under terms of EUA <u>+By Day 90:</u> -Submit any request for exemptions or variance from QS requirements	Upon EUA Declaration Termination
Enforcement Policy (EP)	Expiration of section 319 PHE declaration OR ≥ 45 days after guidance finalization whichever is greater (May 11, 2023)	Continue marketing under terms of EP <u>+Beginning Day 1:</u> -21 CFR 803 (adverse events reporting) <u>+Beginning Day 90:</u> -21 CFR 806 (reports of removals and corrections) -21 CFR 807 Subparts B-D (registration and listing) <u>+By Day 90:</u> -Submit any request for exemption or variance from QS requirements	Upon Withdrawal of Enforcement Policy Guidances

CDRH: Center Initiatives

- Electronic Submission Template And Resource (eSTAR)
- Customer Collaboration Portal (CDRH Portal)
- Total Product Life Cycle Advisory Program Pilot (TAP)
- Medical Device Development Tools (MDDT)
- Predetermined Change Control Plans for Devices
- Cybersecurity in Medical Devices

eSTAR
electronic Submission Template And Resource

- Voluntary use now for submission of 510(k) and De Novo requests
  - Mandatory starting October 2023
- Dynamic PDF template for assembling submission
  - eSTAR is a submission preparation template, NOT a new type of 510(k)
- Guides the medical device applicant through the process of preparing a comprehensive medical device submission
  - Contains automation, guides, integrated databases, policies and procedures in a single package
- Modeled after the SMART review template used by review staff
- 2 eSTAR templates (nIVD and IVD eSTARs) posted online

Electronic Submission Template for Medical Device 510(k) Submissions: Guidance for Industry and FDA Staff

Customer Collaboration Portal (CDRH Portal)

- CDRH submission hub for 510(k)s and De Novos for internal and external stakeholders
- Online progress tracker dashboard displays near real-time submission status
- We have received over 9919 premarket submission through the portal
  - ➢9204 in eCopy and 715 in eSTAR
- Starting October 1, 2023, all 510(k) submissions, unless exempted*, must be submitted as electronic submissions using the electronic Submission Template And Resource (eSTAR)

*See Section VI.A. Waivers and Exemptions from Electronic Submission Requirements of Electronic Submission Template for Medical Device 510(k) Submissions guidance

Send and Track Medical Device Premarket Submissions Online: CDRH Portal

Total Product Life Cycle Advisory Program (TAP) Pilot

- TAP is intended to:
  - Help ensure that U.S. patients have access to high-quality, safe, effective, and innovative medical devices first in the world for years to come by promoting early, frequent and strategic communications between the FDA and medical device sponsors
- The TAP Pilot is one of the commitments agreed to between the FDA and industry as part of the MDUFA reauthorization. It is intended to:
  - Demonstrate the feasibility and benefits of process improvements to the FDA's early interactions with participants and stakeholders that support the vision for TAP
  - Facilitate improved strategic decision-making during device development
  - Collaborate to better align expectations for evidence generation, improve submission quality, and improve the efficiency of the pre-market review process

Total Product Life Cycle (TPLC) Advisory Program (TAP) Pilot

Medical Device Development Tools (MDDT)

A way for the FDA to qualify tools that medical device sponsors can choose to use in the development and evaluation of medical devices.

- Three Categories of MDDTs:
  - Clinical Outcomes Assessment (COA)
  - Biomarker Test (BT)
  - Non-Clinical Assessment Model (NAM)

- The FDA created the voluntary MDDT program to:
  - Advance innovation
  - Increase predictability for medical device sponsors
  - Improve efficiency and transparency
  - Encourage collaboration in developing tools and supporting evidence

Medical Device Development Tools (MDDT)

Predetermined Change Control Plans for Devices

- 2022 Omnibus Appropriations Bill
  - Amends section 515 of the FD&C Act so that changes to a device consistent with an approved predetermined change control plan do not require a supplemental application.
  - FDA may also require that change control plans include labeling required for safe and effective use of the device
- This provision applies to all devices—it is not specific to software or devices with special controls. It applies to both premarket approval and 510(k) applications.
- Predetermined change control plans describe planned changes that may be made to the device (and that would otherwise require a supplemental application under section 515) if the device remains safe and effective without any change.

Cybersecurity in Medical Devices

- The Consolidated Appropriations Act for 2023 was signed into law December 29, 2022 and includes the Food and Drug Omnibus Reform Act (FDORA)
  - Section 3305 of Omnibus – Ensuring Cybersecurity of Medical Devices
  - Adds New Section 524B of the FD&C Act – Ensuring Cybersecurity of Devices
- Applies to prospective submissions for 'cyber devices' under the 510(k), de Novo, HDE, PDP, and PMA pathways
- Effective 90 days after signing (March 29, 2023)

Why is Cybersecurity Important?

Cybersecurity is a part of Safety and Effectiveness

FDA has found 510(k) submissions to be “not substantially equivalent” (NSE) and Premarket Approval (PMA) devices to be “not approvable” based on cybersecurity concerns alone.

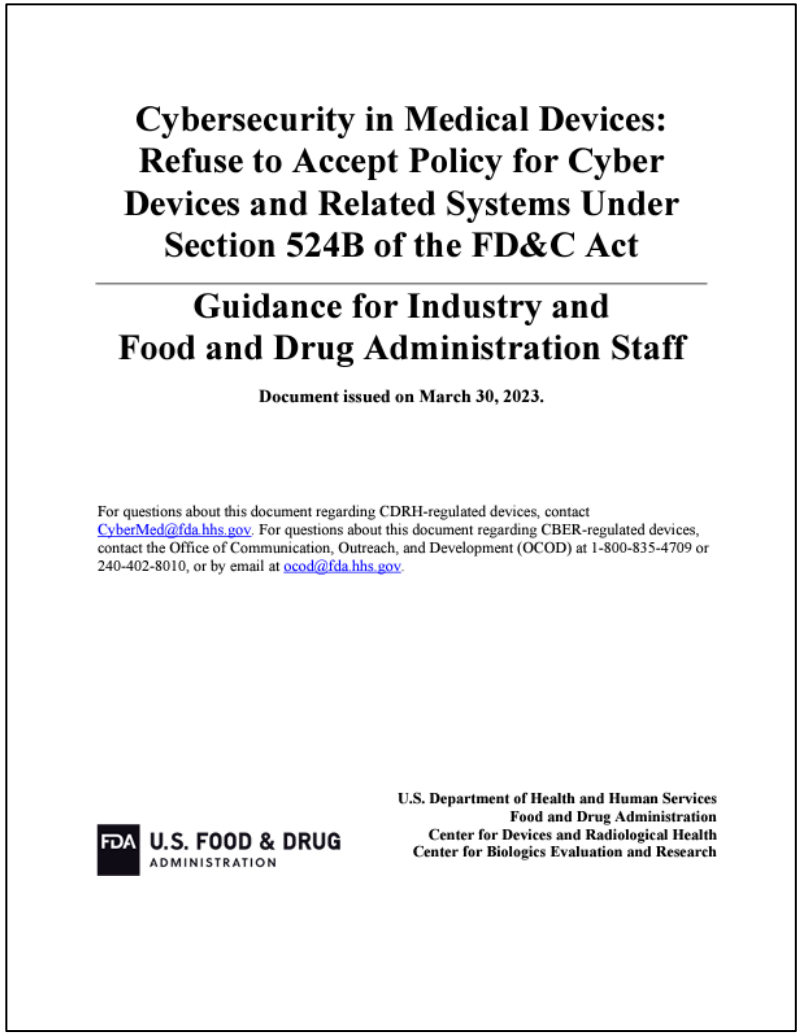
Does Cybersecurity Apply?

- Cybersecurity applies if the device is or contains software
- Cybersecurity documentation is required if the device meets the definition of a Cyber Device
- Cybersecurity considerations apply regardless of whether the software or software component was designed by the medical device manufacturer or a third-party
- Risks **increase** if device contains one or more of these interfaces:
  - Wired: USB, ethernet, SD, CD, RGA, etc. or
  - Wireless: Wi-Fi, Bluetooth, RF, inductive, Cloud, etc.
- Cybersecurity considerations apply for entire system, not just end device. Examples include:
  - Software update infrastructure
  - Cloud applications
  - Commercial devices (phones, tablets, computers, etc.)

https://www.fda.gov/medical-devices/digital-health-center-excellence/cybersecurity-medical-devices-frequently-asked-questions-faqs

FDA Cybersecurity RTA Guidance

- For premarket submissions submitted for cyber devices before October 1, 2023, FDA generally intends not to issue "refuse to accept" (RTA) decisions based solely on information required by section 524B of the FD&C Act.
- Instead, FDA intends to work collaboratively with sponsors of such premarket submissions as part of the interactive and/or deficiency review process.
- Beginning October 1, 2023, FDA expects that sponsors of cyber devices will have had sufficient time to prepare premarket submissions that contain information required by section 524B of the FD&C Act, and FDA may RTA premarket submissions that do not.



Cybersecurity in Medical Devices: Refuse to Accept Policy for Cyber Devices and Related Systems Under Section 524B of the FD&C Act

Guidance for Industry and Food and Drug Administration Staff

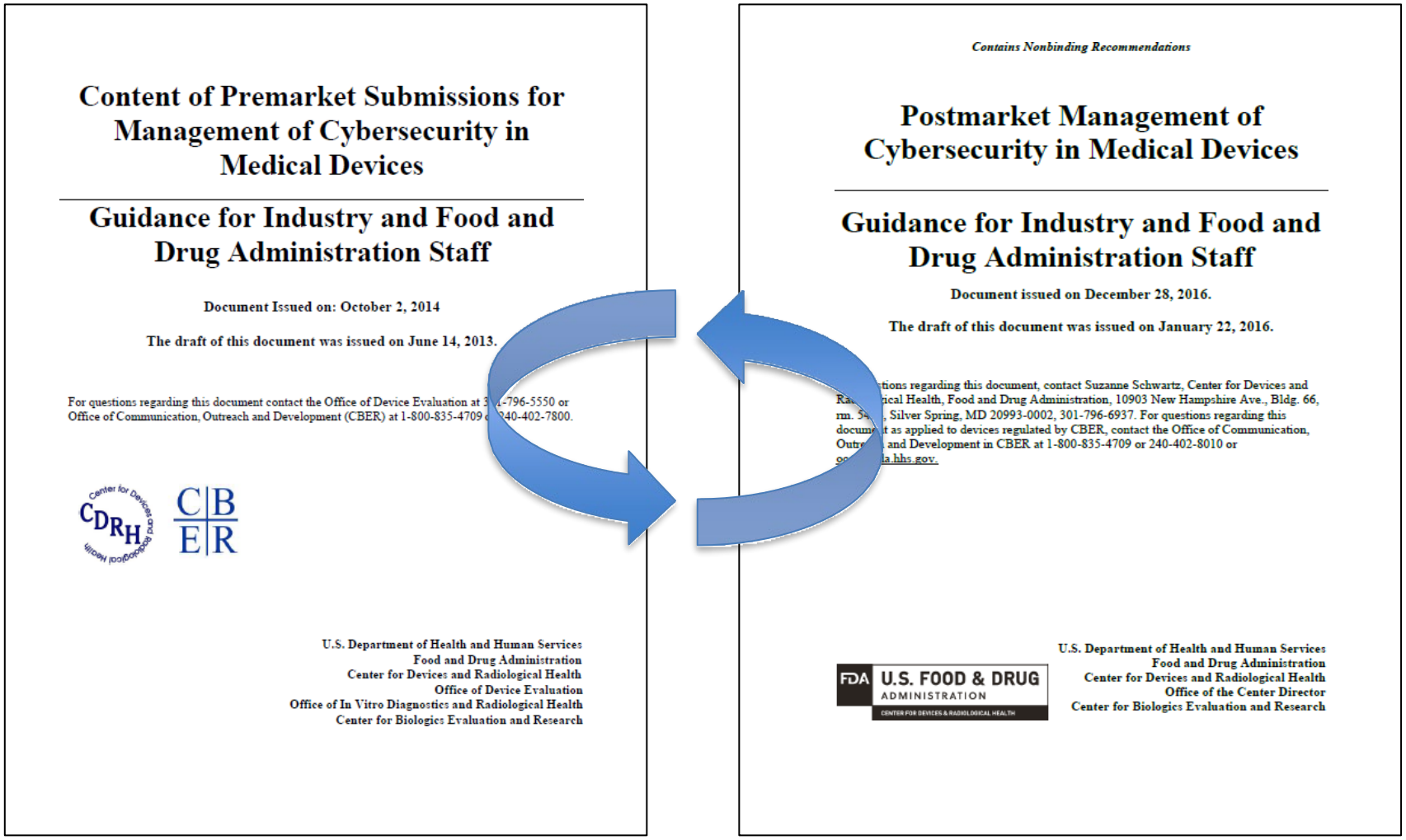
Document issued on March 30, 2023.

For questions about this document regarding CDRH-regulated devices, contact CyberMed@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

FDA Final Cybersecurity Guidance



Content of Premarket Submissions for Management of Cybersecurity in Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document Issued on: October 2, 2014

The draft of this document was issued on June 14, 2013.

For questions regarding this document contact the Office of Device Evaluation at 3[illegible]-796-5550 or Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 o[illegible]240-402-7800.

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

Contains Nonbinding Recommendations

Postmarket Management of Cybersecurity in Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 28, 2016.

The draft of this document was issued on January 22, 2016.

[illegible]tions regarding this document, contact Suzanne Schwartz, Center for Devices and Ra[illegible]ical Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5[illegible], Silver Spring, MD 20993-0002, 301-796-6937. For questions regarding this docum[illegible]t as applied to devices regulated by CBER, contact the Office of Communication, Outr[illegible] and Development in CBER at 1-800-835-4709 or 240-402-8010 or o[illegible]a.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of the Center Director
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Thank You