Point of Care – Conversion of EUA to 510(k)/De Novo

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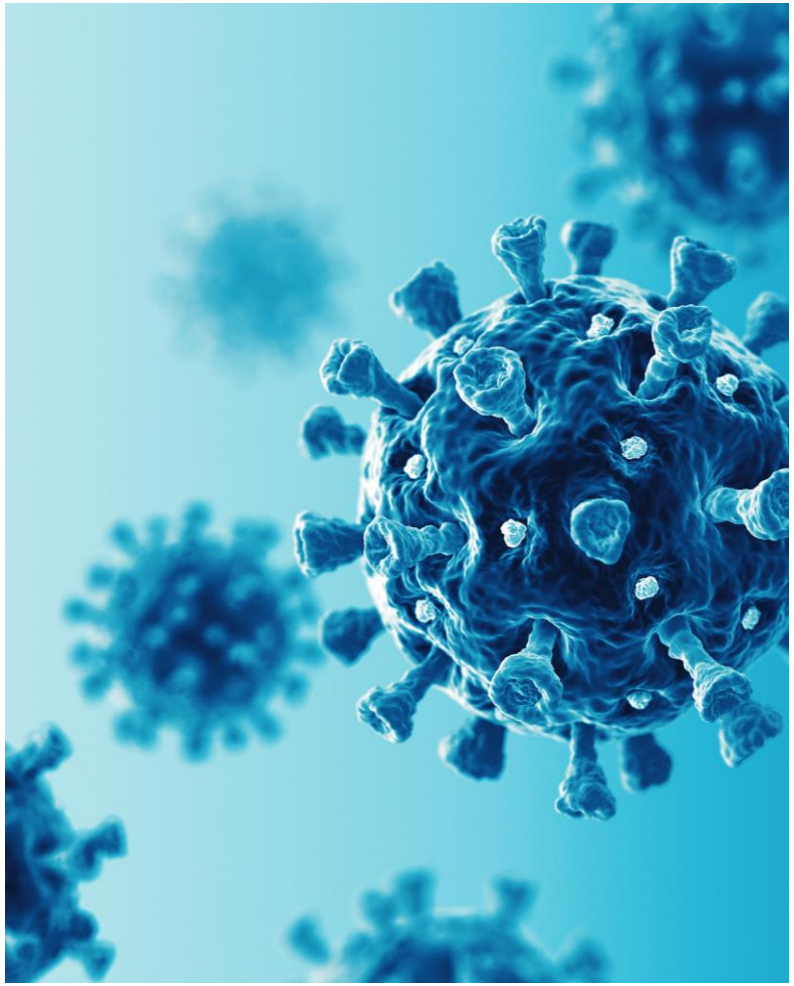
COVID-19 Public Health Emergency (PHE) Determination



January 31, 2020 - The Secretary of Health and Human Services (HHS) issued a declaration of a Public Health Emergency (PHE) related to COVID-19 in accordance with section 319 of the Public Health Service Act (PHS Act).

- 90-day declaration that may be extended
- Does not enable FDA to issue Emergency Use Authorizations (EUA's) [1]

February 9, 2023 - The HHS Secretary renewed the section 319 PHE declaration related to COVID-19.

May 11, 2023 - The section 319 PHE declaration related to COVID-19 expired. [1]

564 Determination

On February 4, 2020, under section 564 of the FD&C Act, the HHS Secretary determined that there is a public health emergency that involves the virus that causes COVID-19 and that it has a significant potential to affect national security. [1]

- The 564 determination enables FDA to issue an Emergency Use Authorization (EUA)
- Authorizes the emergency use of an unapproved product or an unapproved use of an approved product for certain emergency circumstances. (EUA Declaration) [2]

HHS issued four EUA declarations:

- In vitro diagnostics;
- Personal respiratory protective devices;
- Medical devices and alternative products used as medical devices; and
- Drugs and biological products. [1]

Importance of IVDs During the COVID-19 Pandemic

EUA's were issued for SARS-CoV-2 diagnostic tests based on "the totality of scientific evidence, the product may be effective for such use, the known and potential benefits outweigh the known and potential risks for such use, and that there are no adequate, approved, and available alternatives." [2]

- Diagnostic tests played an important role during the pandemic for early detection and treatment as well as in the prevention of the spread of disease.
- EUAs were necessary to expand the supply of IVDs for SARS-CoV-2 when cleared/approved tests were not available and as public need increased.
- Types of COVID-19 related IVDs issued EUAs:
  - Diagnostic Tests
  - Serology/Antibody and Other Adaptive Immune Response Tests
  - Tests for Management of COVID-19 Patients [4]

Emergency Use Authorizations (EUAs)

FDA's FAQs on Emergency Use Authorizations (EUAs) for Medical Devices Related to COVID-19 states, "An EUA declaration under section 564 of the FD&C Act is distinct from, and is not dependent on, a public health emergency (PHE) declaration under section 319 of the Public Health Service Act (PHS Act). Therefore, an EUA may remain in effect beyond the expiration of a PHE declaration if other statutory conditions are met." [5]

- COVID-19 related EUAs remain authorized as long as the EUA declaration and determination under which it was issued remains in effect. [1]
- However, with the expiration of the 319 PHE declaration related to COVID-19 on May 11, 2023, manufacturers are anticipating an announcement of termination of the Section 564 EUA Declaration and are preparing for transition from EUA to a traditional marketing authorization.

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FDA EUA Transition Guidance

- Applies to devices that have been issued an emergency use authorization (EUA) related to COVID-19 under section 564 of the FD&C Act.
- Describes FDA's transition policy for devices issued EUAs and recommendations for submitting device marketing submissions and other actions with respect to these devices. [2]

Contains Nonbinding Recommendations

Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19)

Guidance for Industry, Other Stakeholders, and Food and Drug Administration Staff

Document issued on March 27, 2023.

The draft of this document was issued on December 23, 2021.

For questions about this document, contact the Regulation, Policy, and Guidance Staff at RPG@fda.hhs.gov. For general questions about emergency use authorizations, contact the Office of the Commissioner/Office of the Chief Scientist/Office of Counterterrorism and Emerging Threats at AskMCMi@fda.hhs.gov.

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Transitioning from EUA to a Traditional Marketing Submission

- FDA recognizes that it will take stakeholders time to adjust to normal operations after the termination of the device EUA declarations.
- Under section 564(b), the HHS Secretary is required to provide advance notice that an EUA declaration will be terminated. When an EUA declaration is terminated, all EUAs issued under that declaration also terminate. After an EUA declaration terminates, the emergency use of all products under the EUA declaration are no longer authorized.
- HHS intends to publish the advance notice of termination of each EUA declaration 180 days before the day on which the EUA declaration is terminated.
- FDA recommends that manufacturers submit their 510(k) or De Novo submissions to FDA with sufficient time for the submission to be accepted by FDA before the EUA termination date. The marketing submission should be administratively complete in that it includes all the information necessary for FDA to conduct a substantive review

U.S. Food and Drug Administration. "Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19) [2]

Slide copied from FDA Virtual Town Hall Series – COVID-19 Test Development and Validation [3]

EUA Transition Guidance: 180-Day Advance Notice of Termination

- **Prior to advance notice of termination:**
  - **Comply** with the terms of the devices' respective EUAs
  - **Plan** post-EUA regulatory and disposition strategies
  - **Begin preparation of any required marketing submission** with a **Transition Implementation Plan** if intending to continue distribution of devices after EUA termination
  - Consider **initiating discussions with the Agency** (for example, Pre-Submissions)
- **90-day period after advance notice of termination:**
  - Manufacturers that intend to continue distribution of their devices after EUA termination and that have unique compliance considerations regarding QS requirements may **request an exemption or variance** from a device QS requirement
- **180-day period between advance notice of termination and the EUA termination date:**
  - **Continue to comply** with the terms of the devices' respective EUAs
  - **Submit marketing submission to FDA** with a **Transition Implementation Plan** and have it accepted before the EUA termination date if intending to continue distribution of devices after EUA termination
- **EUA termination date:**
  - 180 days after advance notice of termination; EUAs issued under that EUA declaration will be **terminated**
  - **Enforcement policy** for **devices with marketing submission under review** by FDA
  - **Discontinue distribution** on EUA termination date **if no marketing submission** or on date of **negative decision on marketing submission** (or date manufacturer withdraws or fails to provide a complete response)
  - **Enforcement policy** for **already distributed devices**

12

Distribution of EUA Devices

- FDA expects manufacturers to discontinue distribution of a device within the scope of the guidance:
  - On the EUA termination date, if the manufacturer has not submitted a required marketing submission for its device which is accepted by FDA before the EUA termination date; or
  - On the date the manufacturer receives a negative decision on its marketing submission as FDA's final action, or on the date the submission is withdrawn, or if the manufacturer fails to provide a complete response to an FDA request for additional information within the allotted time identified in FDA's letter.
- FDA does NOT intend to object to the continued distribution of devices within the scope of the guidance after the EUA termination date where:
  - The manufacturer has submitted a marketing submission to FDA, and it is accepted by FDA before the EUA termination date; and
  - FDA has not taken a final action on the marketing submission. [2]

U.S. Food and Drug Administration. "Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19) [2]

Transition Implementation Plan

FDA recommends that the Transition Implementation Plan include the following information:

1. Estimated number of devices under an EUA that are currently in U.S. distribution
2. An explanation of the manufacturer's benefit-risk based plan for disposition of already distributed product in the event of a **negative decision** on the marketing submission. If the manufacturer is proposing to leave already distributed product in place, the plan should address the rationale for doing so and considerations such as the following, where relevant:
   - Process for notifying patients, consumers, healthcare facilities, healthcare providers, and device distributors of the device's regulatory status;
   - Process and timeline for restoring already distributed devices to an FDA-cleared or -approved version;
   - Process and timeline for providing a physical and/or electronic copy of updated labeling that accurately describes the product features and regulatory status (e.g., that the product lacks FDA clearance, approval, or authorization) for reusable devices, and
   - A description of the maintenance plan for already distributed devices.
3. An explanation of the manufacturer's plans for addressing already distributed product in the event of a **positive decision** on the marketing submission, including considerations such as the following, where relevant:
   - Process for notifying patients, consumers, healthcare facilities, healthcare providers, and device distributors of the device's regulatory status; and
   - Process and timeline for providing to users of already distributed devices updated labeling or components for the cleared or approved device, including updated labeling or components to reflect any cleared/approved changes to the already distributed device.

U.S. Food and Drug Administration. "Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19) [2]

Resources/Tools:

1. FDA Guidance/Recommendations for PMN
   - Recommendations on validation studies to support a premarket submission for SARS-CoV-2 diagnostic tests (Molecular and Antigen Tests)
2. FDA 510(k) Premarket Notification and *De Novo* summary databases
3. Gap Analysis
   - *Does the device meet FDA standards for safety and effectiveness?*
     Compare details of studies conducted for EUA submissions with 510(k)/*De Novo* submission requirements. (Bench testing, animal testing, clinical testing, software validation, etc.)
   - *Will your device be competitive on the market?*
     Compare device sensitivity and specificity with assays already on the market and published studies [6]
4. Pre-Submission
   - Collaborate with FDA early in the process to discuss validation study proposals and recommendations for 510(k)/*De Novo*
5. Real World Data (RWD)
   - Real-world data obtained from use of the IVD under the EUA may be submitted in support of a marketing submission[2]
6. Quality System Regulation
   - Are Quality Management System and design control requirements under 21 CFR 820 met?

Real-World Evidence

FDA encourages the use of Real-World Data (RWD) and Real-World Evidence (RWE) to support marketing submissions for SARS-CoV-2 diagnostic tests. [3]

- Information on the performance of the device with various sample types and across multiple operators
- Reduces the amount of testing the developer will need to do
- Challenges in obtaining appropriate RWD

National Evaluation System for Health Technologies (NEST) Implementation Cases [3]

- Project for analyzing data from COVID-19 diagnostic tests
- Contact FDA for information about leveraging this data
- Email Covid19DX@fda.hhs.gov or submit a pre-Sub

SHIELD Project (Systemic Harmonization and Interoperability Enhancement for Laboratory Data)

- Collaboration aimed at building and implementing data systems to support the exchange of data in the US [7]
- Developers will be able to gather and analyze real-world data from diagnostic tests, expediting the pre-market review of the tests and assessment of post-market performance. [7]
- FDA recommends developers to reach out through Q-Sub process to discuss your approach for the use of this RWD in a submission [3]

QMS Requirements

Current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 (design, manufacture, packaging, labeling, storage, and distribution of the device) may have been waived during EUA.

After the EUA termination date, the manufacturer is expected to comply with QSR for an EUA authorized test while a marketing submission is under FDA review.

Manufacturers who face unique compliance considerations regarding QSR may request an exemption or variance from the QSR requirements. (21 CFR 820.1(e))

- Must be requested within 90 days of publication of the advance notice of termination of the EUA declaration. [2]
- FDA will make case-by-case decisions on compliance and enforcement. [3]

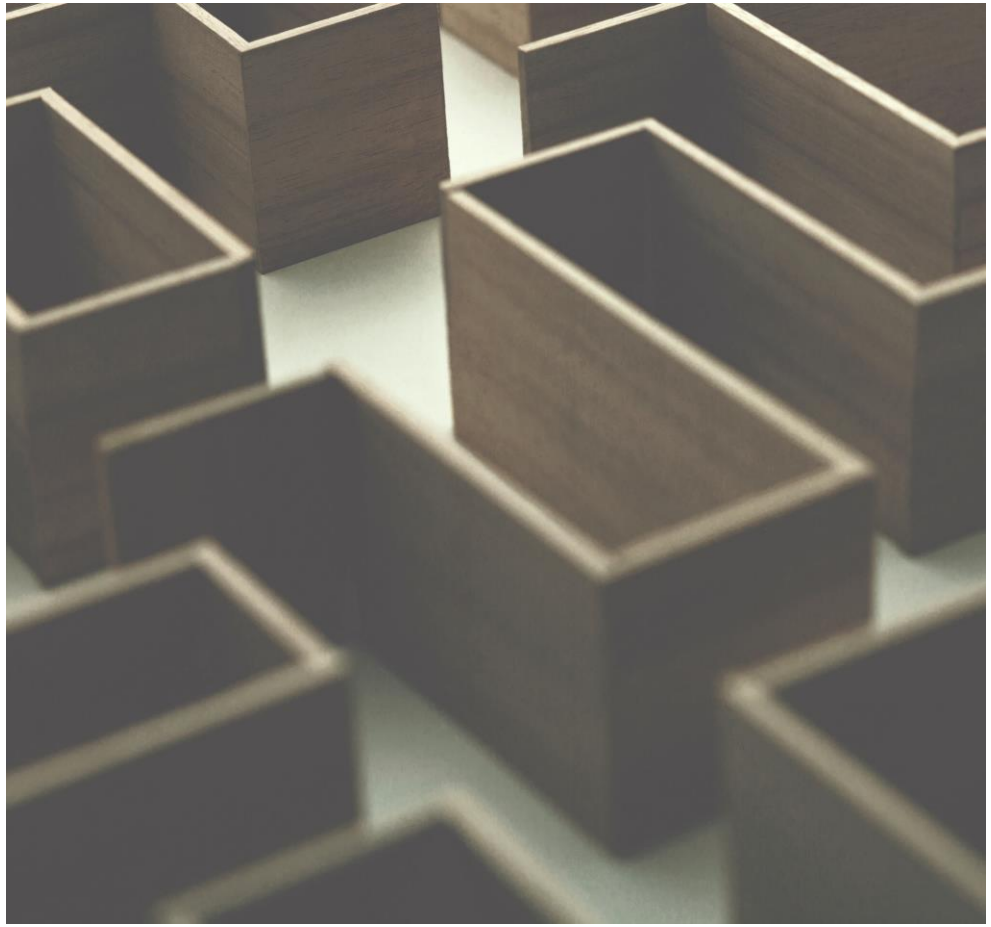
Point-of-Care (PoC) Tests

- Various testing environments and operators
  - Urgent care facilities- doctors, nurses, PAs
  - Physician's office- nurses, PAs, office staff
  - Pharmacies- pharmacists, pharmacy technicians
- States of health of patients may affect test performance
  - Symptomatic or asymptomatic
  - Patient state of health
  - Medications
- Risk of an incorrect result with PoC tests
  - Less sensitive than lab tests
  - Testing performed in less controlled environment
  - Specimen/Reagent control
  - Untrained operators
  - Risk control measures
- POC Performance Validation
  - Performance studies (sensitivity, specificity, interference, repeatability)
  - Flex studies based on risk analysis
  - Usability studies with intended user testing entire workflow
  - Stability and shipping studies
  - Clinical studies /reproducibility conducted at CLIA waived sites [8]
- Instructions for Use
  - Simple and Clear [8]

IVDs and CLIA Categorization and Waivers

- Authorization under EUA for a specific setting is only effective during the duration of the EUA declaration. [3]
- For IVDs authorized under an EUA to perform moderate complexity tests in laboratories certified under CLIA, FDA intends to categorize the test's complexity immediately following FDA's final action on the marketing submission, following FDA's typical categorization process. [2]
- For IVDs authorized under an EUA for use in patient care settings under a CLIA Certificate of Waiver, FDA intends to accept marketing submissions under the Dual 510(k) and CLIA Waiver by Application pathway, or Dual De Novo and CLIA Waiver marketing submissions, as appropriate. [2]
- For IVDs authorized under an EUA for home use, if a marketing submission for such test is subsequently cleared, approved, or authorized for home use, the test will be waived by regulation under 42 CFR 493.15(c), meaning that the test will be categorized as waived and a CLIA Waiver by Application is not required. [2]
- However, tests that are cleared or approved for home use may not be referred to as "CLIA waived" because they have not received CLIA Waiver by the application process.
- To reduce the potential for disruption in IVD distribution and use, FDA recommends that any marketing submission that needs a CLIA categorization decision be submitted as soon as possible to facilitate FDA's review of both the marketing submission and CLIA categorization request, or CLIA Waiver by Application, prior to the termination of the EUA declaration. [2]

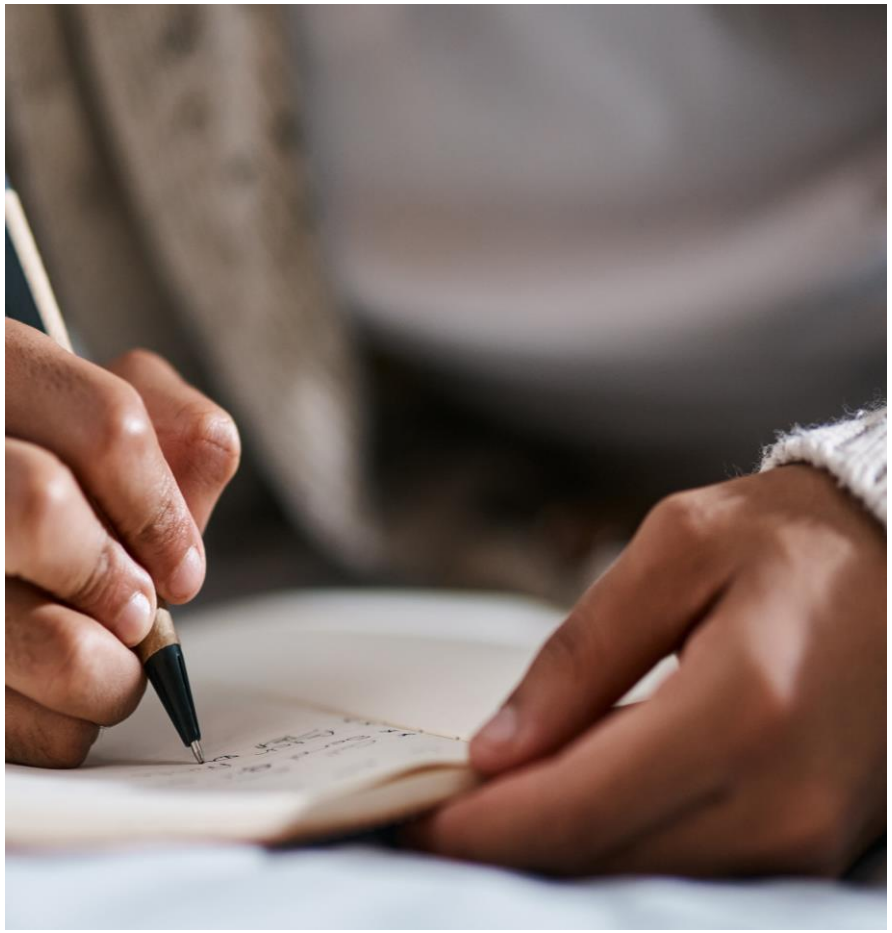
Challenges



1. Expanded validation study requirements for 510(k)/*De Novo* submissions compared to EUA
2. Changes or updates to the device compared to the EUA product
   - Add new intended use or user, change from singleplex to multiplex test, etc.
   - Additional testing and longer time to submission
   - If using EUA studies, need to justify why each EUA study is valid for the current test configuration
3. Demonstrating Substantial Equivalence to a predicate device for a SARS-CoV-2 assay 510(k) submission
   - Benefit-risk analysis for different technological characteristics
4. New and changing recommendations for studies required for premarket submissions (i.e., COVID-19 variant testing)

Lessons Learned

1. Conduct a thorough gap analysis
   - Study design- number of samples and lots tested, concentration levels, unbiased, flex studies for identified risks
2. Comparison to predicate
   - Performance
   - Intended use and intended user
3. Plan and prepare early
   - Manufacturers should submit marketing submission as early as possible to get it accepted by FDA before the EUA is terminated [2]
   - Marketing applications that need a CLIA categorization will require additional time to review the marketing submission and the CLIA categorization request prior to the termination of the EUA declaration [2]
   - Unexpected delays in product development process
4. Have a clear transition plan
   - Specify number of days from a positive/negative decision activities will begin and whether the plan changes if EUA termination date falls after this time
   - Include plan for product in distribution, in warehouse, in-process (EUA and 510(k) device inventories), rework, labeling
5. FDA is continuously assessing their requirements for marketing submissions for COVID-19 IVDs
   - Use the Pre-Sub process to discuss details of study design when unsure of current FDA expectations.



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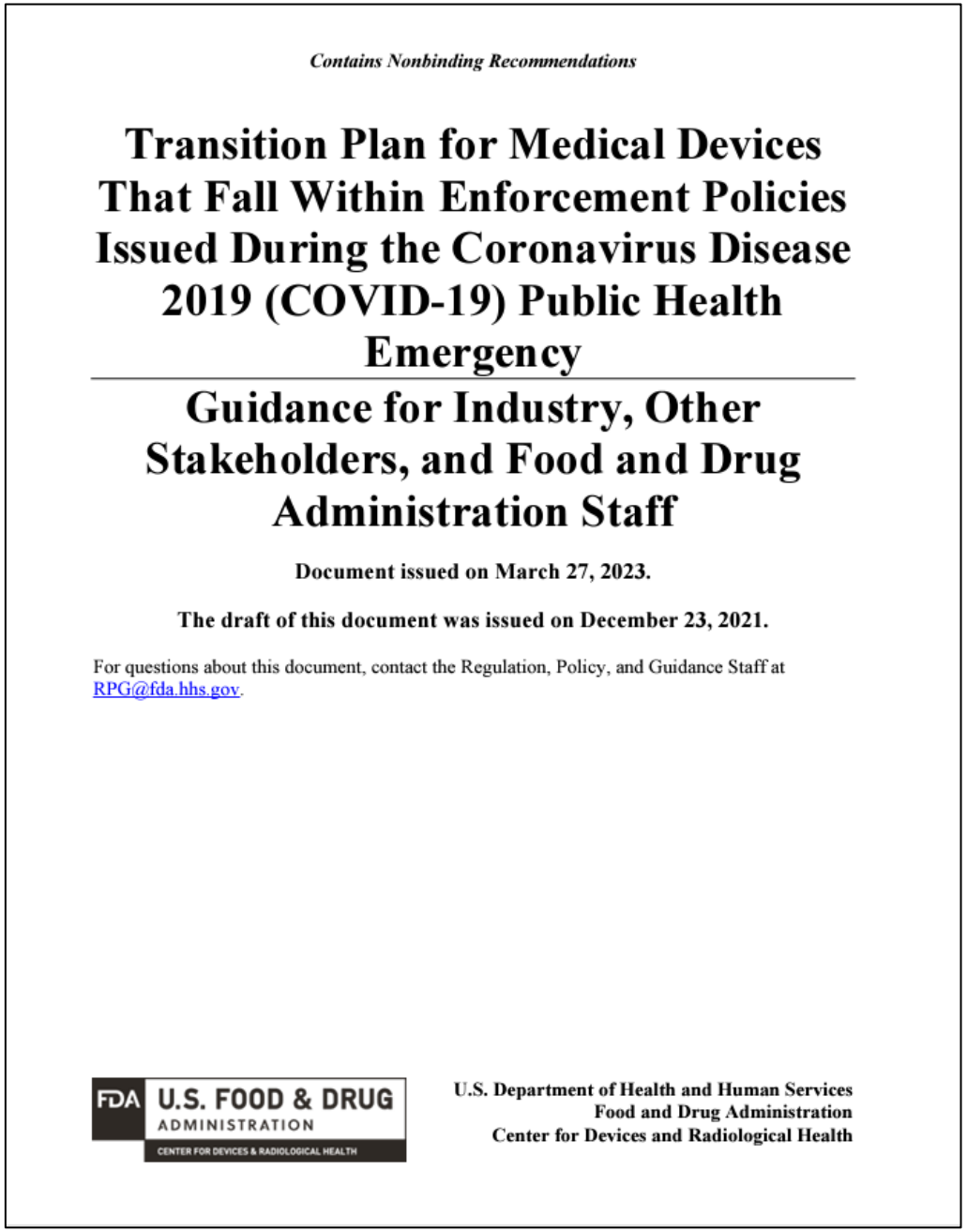
Companion Transition Guidance for Devices that Fall within Enforcement Policies Issued During the COVID-19 PHE

IVDs that fall within enforcement policies issued during the COVID-19 PHE are within the scope of this guidance:[3]

- Enforcement Policy for Remote Digital Pathology Devices During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
- Enforcement Policy for Modifications to FDA Cleared Molecular Influenza and RSV Tests During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
- Coagulation Systems for Measurement of Viscoelastic Properties: Enforcement Policy During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
- Enforcement Policy for Viral Transport Media During the COVID-19 Public Health Emergency



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Thank you