Transitioning Diagnostics from Emergency Use Authorization (EUA) to Marketing Applications

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OPEQ, CDRH

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Overview

• Emergency Use Authorization (EUA) authority
• EUA vs. Premarket Study Requirements
• RWE/RWD Guidance
Emergency Use Authorization (EUA) Authority
EUA Authority

• Section 564 of the Federal Food, Drug and Cosmetic Act (FD&C Act)
  – Amended by the Project Bioshield Act of 2004
  – Amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)
  – The 21\textsuperscript{st} Century Cures Act of 2016
  – Public Law 115-92 of 2017
EUA Authority

FDA can authorize:

• Use of unapproved MCMs (despite lacking the amount of data that would be necessary for approval)
• Unapproved use of approved MCMs (e.g., for a new indication)

to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when certain criteria are met.
EUA and IVD

• In vitro diagnostics play a very important role in any emergency response involving an emerging infectious disease - from initial outbreak detection, diagnosis, patient management and infection control.

• In the absence of a cleared/approved FDA assay the EUA authority is a mechanism FDA can use to address a public health emergency.
<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Declared Date</th>
<th>Emergency Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza H7N9</td>
<td>Orthomyxoviridae</td>
<td>April 19, 2013</td>
<td>Emergency Use of In Vitro Diagnostics for Detection of the Avian Influenza A (H7N9) Virus</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Coronaviridae</td>
<td>May 29, 2013</td>
<td>Emergency Use of In Vitro Diagnostics for Detection of Middle East Respiratory Syndrome Coronavirus</td>
</tr>
<tr>
<td>Ebola</td>
<td>Filoviridae</td>
<td>August 4, 2014</td>
<td>Emergency Use of In Vitro Diagnostics for Detection of Ebola Virus</td>
</tr>
<tr>
<td>Enterovirus D68</td>
<td>Picornaviridae</td>
<td>February 6, 2015</td>
<td>Emergency Use of New In Vitro Diagnostics for Detection of Enterovirus D68</td>
</tr>
<tr>
<td>Zika Virus</td>
<td>Flaviviridae</td>
<td>February 26, 2016</td>
<td>Emergency Use of In Vitro Diagnostic Tests for Detection of Zika Virus and/or Diagnosis of Zika Virus Infection</td>
</tr>
<tr>
<td>2019-nCoV</td>
<td>Coronaviridae</td>
<td>January 31, 2020</td>
<td></td>
</tr>
</tbody>
</table>
**EUA Determination and Declaration**

- **DOD SECRETARY**
  - Determination of Military Emergency or Significant Potential for Military Emergency

- **DHS SECRETARY**
  - Determination of Domestic Emergency or Significant Potential for Domestic Emergency

- **HHS SECRETARY**
  - Determination of Public Health Emergency or Significant Potential for Public Health Emergency

- **DHS SECRETARY**
  - Identification of Material Threat

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**HHS SECRETARY**
- Declaration that Circumstances Exist Justifying the EUA

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**FDA COMMISSIONER**
- Issuance of EUA (if criteria for issuance met)

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**Consultation with ASPR, CDC, NIH**

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**Termination of Declaration & EUA**
Criteria for EUA

1. The agent causes a serious or life-threatening disease or condition.

2. Based on totality of scientific evidence, reasonable belief:
   • Product may be effective
   • Known/potential benefits outweigh known/potential risks

3. No adequate, approved, available alternative to the product
EUA program within FDA
OPEQ/OHT7-OIR EUA Program

1. Pre-EUA Submission
2. EUA Submission
3. Emergency Use Authorization
4. EUA Amendments Granted

EUA Documents:
- EUA Review Template
- Letter of Authorization
- Fact Sheets – Healthcare Providers and Patients
- Manufacturer Package Insert/Instructions for Use

Public Documents:
- Fact Sheets – Healthcare Providers and Patients
- Manufacturer Package Insert/Instructions for Use
EUA vs. Premarket Study Requirements
# EUA vs. Premarket: In Vitro Diagnostics

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Emergency Use Authorization (EUA)</th>
<th>De Novo/510(k)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Special Circumstances</strong></td>
<td>Requires declaration by the HHS Secretary that circumstances exist justifying the EUA; There is no adequate, approved, and available alternative to the product</td>
<td>No</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Temporary - remains in effect for the duration of the declaration unless revoked sooner</td>
<td>Not Limited</td>
</tr>
<tr>
<td><strong>Analytical Evaluation</strong></td>
<td>Limited</td>
<td>Full validation</td>
</tr>
<tr>
<td><strong>Clinical Evaluation</strong></td>
<td>Limited</td>
<td>Full validation</td>
</tr>
<tr>
<td><strong>cGMP</strong></td>
<td>Expected but limits or waivers may be granted in an EUA on a case-by-case basis</td>
<td>Required</td>
</tr>
</tbody>
</table>

[https://www.fda.gov/about-fda/cdrh-transparency/evaluation-automatic-class-iii-designation-de-novo-summaries](https://www.fda.gov/about-fda/cdrh-transparency/evaluation-automatic-class-iii-designation-de-novo-summaries)
# Studies EUA vs. De Novo/510(k) - NAAT

<table>
<thead>
<tr>
<th>NAAT</th>
<th>Emergency Use Authorization (EUA)</th>
<th>De novo/510(k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limit of Detection (LoD)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inclusivity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Some in silico</td>
<td>Some in silico</td>
</tr>
<tr>
<td>Exclusivity</td>
<td>Limited</td>
<td>Full validation</td>
</tr>
<tr>
<td></td>
<td>Some in silico</td>
<td>Some in silico</td>
</tr>
<tr>
<td>Interference</td>
<td>Situation specific</td>
<td>Yes</td>
</tr>
<tr>
<td>Precision</td>
<td>No</td>
<td>Yes - Multisite</td>
</tr>
<tr>
<td>Fresh vs. Frozen</td>
<td>Fresh specimens preferred</td>
<td>Fresh specimens preferred</td>
</tr>
<tr>
<td>Clinical Evaluation</td>
<td>Limited – natural clinical specimens</td>
<td>Full validation – natural clinical specimens</td>
</tr>
</tbody>
</table>
### EUA IVD to Full Marketing Status

<table>
<thead>
<tr>
<th></th>
<th>H7N9</th>
<th>MERS-CoV</th>
<th>Ebola</th>
<th>Enterovirus D68</th>
<th>Zika</th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUA Declaration</strong></td>
<td>April 19, 2013</td>
<td>May 29, 2013</td>
<td>August 4, 2014</td>
<td>February 6, 2015</td>
<td>February 26, 2016</td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Original EUA Diagnostics:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>39</strong></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td>20</td>
<td><strong>39</strong></td>
</tr>
<tr>
<td><strong>EUA Re-authorizations and Amendments:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>18/61</strong></td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
<td>31</td>
<td>0</td>
<td>45</td>
<td><strong>45</strong></td>
</tr>
<tr>
<td><strong>De Novo or 510(k) Transitions:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>6</strong></td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>
Guidance for Industry

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
FDA RWE/RWD Guidance

- **RWD** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- **RWE** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.
Regulatory Context in Which RWE May be Used

- RWD used to generate the RWE are of sufficient quality
- May potentially be used as some or all of the evidence necessary for understanding medical device performance at different points in the Total Product Life Cycle (TPLC)
Characteristics of RWD

RWD must demonstrate:

• **Relevance** – is the RWD data adequate to address the applicable regulatory question or requirement

• **Reliability**
  - Data accrual: how the data were collected
  - Data assurance: data quality and integrity
Example where RWE might be used

• Expanded indications of use
• Postmarket surveillance studies
• Post-approval device surveillance as condition of approval
• Control group
• Supplementary Data
• Objective Performance Criteria and Performance Goals
Questions

• Can I use the data obtained for EUA authorization?
  Yes, if no modifications to the device have been made since the EUA authorization. If modifications have been made, a risk assessment of the modifications is required to determine the extend of changes to the device and its influence on performance.

• Can I use data generated outside the US in an FDA submission?
  Yes, if the test procedure was performed according to the package insert with no deviations.
Question

• Can RWD be used to help support the advancement of EUA IVD products to full marketing status?
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- Michael Wiack

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Jay Epstein

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Additional Resources

- FDA Medical Countermeasures Initiative (MCMi)
  - www.fda.gov/medicalcountermeasures

- FDA EUA Website (official updates, current & terminated EUAs, guidance)
  - www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

- FDA Draft Guidance on EUAs and other MCM Emergency Use Authorities

- FDA MCM Emergency Use Authorities Website (official updates)

- FDA Zika Response Updates Website
  - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm (also available in Spanish and Portuguese)

- DMD Contact Information
  - Uwe Scherf, M.Sc., Ph.D., Director, Division of Microbiology uwe.scherf@fda.hhs.gov

- Email Contact for Interactive Review and Guidance
  - CDRH-ZIKA-Templates@fda.hhs.gov