Emergency Use Authorization (EUA) Program Zika Virus Update

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June 2, 2016

Emergency Use Authorization (EUA)

During certain circumstances:

Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the FDA Commissioner may allow

- **use of unapproved medical products** or
- **unapproved uses of approved medical products**

to **diagnose**, treat, or prevent serious or life-threatening diseases or conditions caused by Chemical, Biological, Radiological, or Nuclear (**CBRN**) threat agents when there are **no** adequate, approved/cleared, and available **alternatives**.

Emergency Use Authorization (EUA) (cont. I)

21 U.S. Code § 360bbb–3 - Authorization for medical products for use in emergencies

(c)(2)(A) the **product may be effective** in diagnosing, treating, or preventing—

(c)(2)(B) **the known and potential benefits of the product**, when used to diagnose, prevent, or treat such disease or condition, **outweigh the known and potential risks** of the product

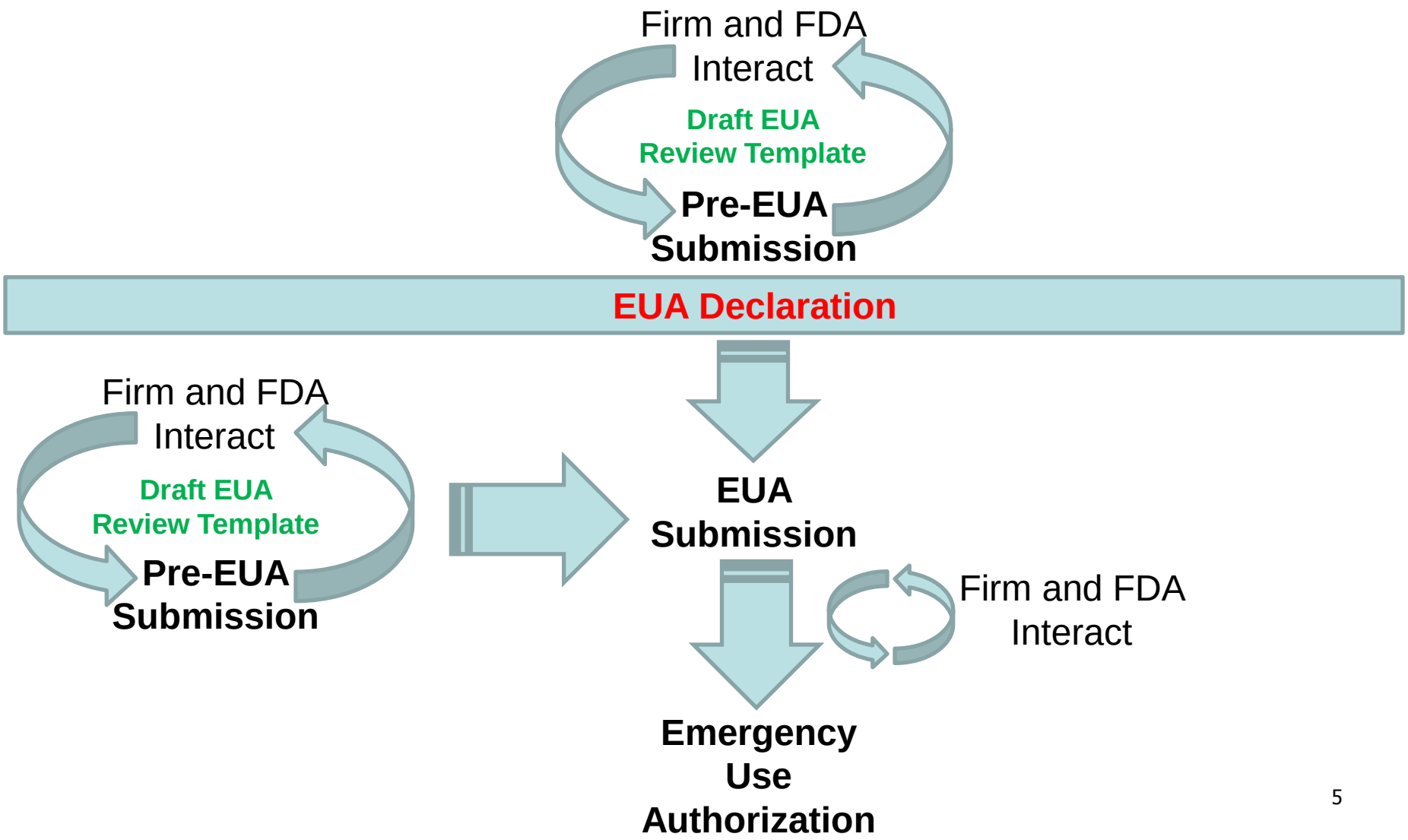
(c)(3) **that there is no adequate, approved, and available alternative to the product** for diagnosing, preventing, or treating such disease or condition

Emergency Use Authorization (EUA) (cont. II)

21 U.S. Code § 360bbb–3 - Authorization for medical products for use in emergencies

- FDA determines the **benefits and risks** of **each product** for which an EUA is requested **independently**.
- Authorization is based on the **totality of available scientific evidence**.
- **Performance criteria based on benefit/risk assessment**, which can be applied to all EUA applications over the entire course of an outbreak or epidemic.
- Compliance with design and **manufacturing control regulation may be waived**
- The letter of Authorization names conditions which must be met. (i.e., periodic reporting, patient fact sheet, and duration).

Emergency Use Authorization (EUA)



EUA Diagnostics in Past and Current Emergencies

	H1N1	H7N9	MERS-CoV	Ebola	Enterovirus D68	Zika
EUA Declaration	April 26, 2009	April 19, 2013	May 29, 2013	August 5, 2014	February 6, 2015	May 31, 2016
EUA Diagnostics:						
Molecular	**17**	**2**	**2**	**9**	**1**	**3**
Antigen	**1**	**1**	**0**	**2***	**0**	
Serology	**0**	**0**	**0**	**0**	**0**	**1**

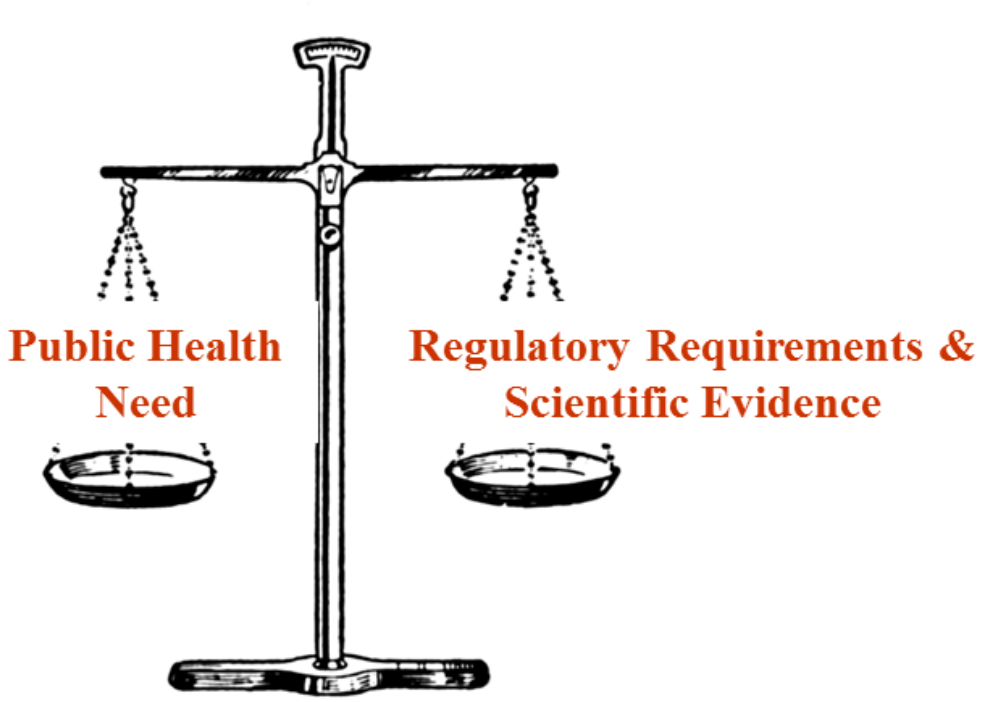
* Includes one product that was authorized for two different intended uses

Note: Around 70 submitted, so far 41 authorized

Draft EUA Review Templates

- Draft **EUA Review Templates** developed to stream line data submission as well as **data review** and review documentation
- **Outlines** FDA's current **recommendations** for the **analytical** and **clinical** validation **studies** needed in support of an EUA submission for an infectious disease IVD
- **Dynamic Template:** Draft document, adapted depending on specific circumstances of the outbreak, Analyte & Technology (e.g., molecular, serology), starting point
- **Assist Sponsors** and **FDA Reviewers**:
  - Manufacturer fills out the template
  - Template serves as basis for interactive review
  - Template will later serve as sponsor's EUA Submission AND
  - Review memorandum

Emergency Use Authorization (EUA)



Analytical Sensitivity
(LoD)

Analytical Specificity
- Reactivity
- Cross reactivity
- Interference

Clinical Evaluation
- Clinical Sensitivity
- Clinical Specificity

Conditions of Authorization

FDA may establish conditions on an EUA **necessary** or appropriate **to protect the public health**. Some conditions are required to the extent practicable given the applicable circumstances of the emergency or threat, whereas others may be imposed entirely at the discretion of FDA.

http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm

Conditions of Authorization (cont. I)

- **Information relating to the EUA Product** – provided in the form of **Fact Sheets** for **healthcare providers** and **patients** (recipients of the test)
- **Monitoring and reporting of adverse events** – required to the extent practicable given the circumstances of the emergency
- **Records** – firm to maintain records and to grant FDA access to records – examples include **number of devices** shipped or sold during EUA

Conditions of Authorization (cont. II)

- **Distribution and use**– conditions may be placed on **who** may **distribute** and **who** may **use** the product, and how distribution and administration are to be performed. In addition, conditions may be placed on the categories of **individuals** to whom, and the circumstances under which, the product **may be administered**.
- **Advertising** – conditions may be placed on advertisements and other promotional printed materials relating to the EUA device

Conditions of Authorization (cont. III)

- **Interim WHO Zika Reference Standard or FDA-recommended Reference Material (CBER):**

[*Sponsor*] will assess traceability of the [*X PCR device*] with the interim WHO Zika reference standard or the FDA recommended reference material. After submission to FDA and FDA's review of and concurrence with the data, [*Sponsor*] will update their labeling to reflect the additional testing.

Duration an EUA

FDA will specify the **effective date of an EUA** issued under section 564.

- In general, an EUA will remain **in effect for** the **duration of the declaration** under which it was issued
- Unless the EUA is **revoked** because the **criteria of issuance are no longer met** or
- **Revocation** is appropriate **to protect public health or safety**

Draft EUA Review Templates - Zika

To request templates contact:

CDRH-ZIKA-Templates@fda.hhs.gov

- Molecular Draft EUA Review Template
- Serological IgM Draft EUA Review Template

Draft EUA Review Template – Content 1

A. **Executive Summary**
B. **Purpose for Submission**
C. **Measurand**
D. **Applicant**
E. **Proprietary and established names**
F. **Product Description**
    - Incl. Device, controls and all accessories
G. **Test Principle**
H. **Proposed Intended Use**
I. **Unmet need addressed by the product**

Draft EUA Review Template – Content 2

J. Approval/Clearance status

K. Product manufacturing

- Manufacturing sites and manufacturer's name for all components and accessories of the device, incl. Components/materials needed but not supplied
- Description of any available quality system, packagers, distributors

L. Approved/cleared alternative products

M. Interpretation of results

- Interpretation of controls
- Examination of patient results
- Interpretation of results

EUA Draft Review Template – Content 3

N. Safety and Effectiveness

Including (depends on the assay):

1. Analytical Sensitivity (LoD)
2. Analytical Specificity
3. Interference
4. Clinical Evaluation

O. Risks and Benefits

- Risks

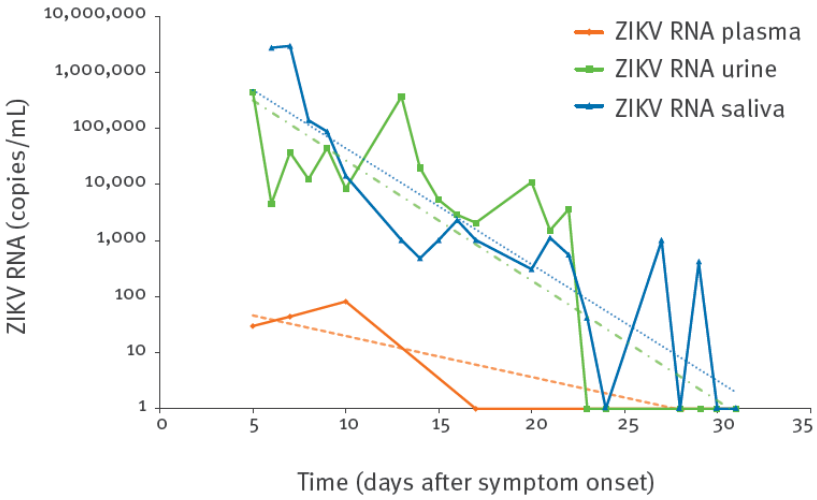
(the risks / benefits section will change depending on the analyte and may change throughout the period of an outbreak)

Zika IVD Issues

- **Molecular IVDs:**
  - Diagnostic Window – very short typically 7 days post symptoms (CDC)

FIGURE 1

Kinetics of ZIKV RNA load measured by quantitative real-time RT-PCR in plasma, urine, and saliva samples of a patient with ZIKV infection, Italy, January 2016



- Musso et al., J. Clinical Virology 2015 Zika virus in salvia – 182 patients – salvia sample increased rate of molecular detection of ZIKV in the acute phase – but did not enlarge the window of detection

- Gourinat et al., Emerging Infec. Diseases 2015 Zika virus in Urine – 6 patients – Higher viral titers for longer periods range 10 days to >20 days depending on individual.

Euro Surveill. 2016;21(10):pii=30159. DOI: http://dx.doi.org/10.2807/1560-7917

Zika IVD Issues (cont. I)

- **Serological IVDs**
  - Cross-reactivity with other Flaviviruses, especially Dengue
  - Secondary infections
  - Stunted IgM response when Zika is a secondary infection

Proposal: IgG assay may help – Likely to require repeat specimens ~ 1-2 weeks apart.

Zika EUA Team

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CBER
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Contact directly for interactive review and regulatory guidance:
CDRH-ZIKA-Templates@fda.hhs.gov
We have many topic specific working groups who are willing to help

http://www.fda.gov/emergencypreparedness/
Information on:

- Crisis management
- Emergency response
- Emerging threats

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/
Disease or condition specific guidance documents state FDA study recommendations.
510(k) database – public disclosure of all device clearance and approvals including data summaries