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OIR, CDRH, FDA

FDA EMERGENCY USE AUTHORIZATION: THE ZIKA VIRUS EXPERIENCE

BARDA Industry Day

October 29-30, 2018 Washington DC

Acknowledgements



DMD EUA Team - OIR/CDRH

FDA CBER

FDA Office of the Commissioner

**Office of Counterterrorism and
Emerging Threats**

FDA Office of Chief Counsel

CDC

CMS

NIH

BARDA/ASPR

WHO

Overview

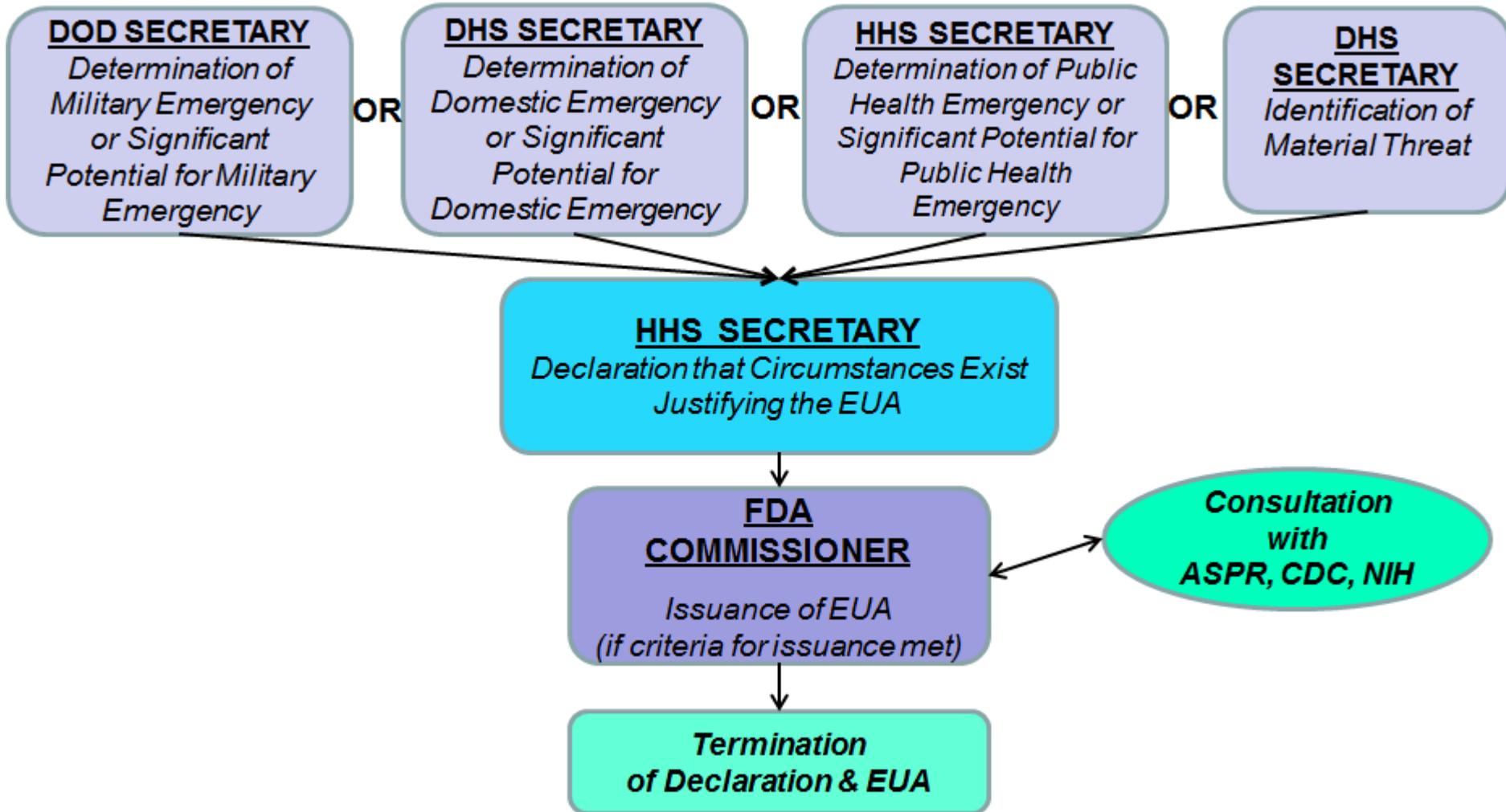


- **The Emergency Use Authorization**
- **IVD and EUAs**
- **DMD EUA Program**
- **IVD EUAs Past and Present**
- **Zika EUAs**
- **EUA After the Storm**
- **Resources**

EUA Authority (FD&C Act § 564)

- With an EUA, 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 and pre-requisites are met**

EUA Circumstances



EUA Authority (FD&C Act § 564)... continued



- **Letter of Authorization** - Conditions of authorization = safeguards, such as:
 - Information on emergency use, including “not FDA-approved”
 - Fact sheets for patients and healthcare providers
 - Record keeping and monitoring of adverse events
 - Collection of information
 - Conditions also clarify roles (e.g., manufacturer, distributors, laboratories)

Final Guidance

Emergency Use Authorization of Medical Products and Related Authorities

Guidance for Industry and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of the Chief Scientist
Office of Counterterrorism and Emerging Threats



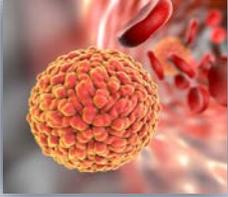
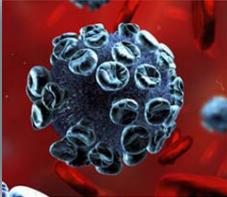
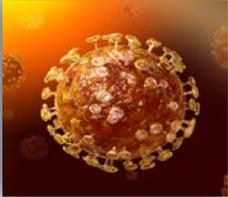
EUA Vs. Premarket: In Vitro Diagnostics



Requirements	Emergency Use Authorization (EUA)	Premarket Notification or Application
Special Circumstances	Requires declaration by the HHS Secretary that circumstances exist justifying the EUA There is no adequate, approved, and available alternative to the product	No
Analytical Evaluation	Limited	Extensive
Clinical Evaluation	Limited	Extensive
Duration	Temporary - remains in effect for the duration of the declaration unless revoked sooner	Not Limited
CGMP	Expected but limits or waivers may be granted in an EUA on a case-by-case basis	Required

HHS Secretary Declaration of Emergency or Threat



Zika Virus <i>Flaviviridae</i>	Enterovirus D68 <i>Picornaviridae</i>	Ebola <i>Filoviridae</i>	MERS-CoV <i>Coronaviridae</i>	Influenza H7N9 <i>Orthomyxoviridae</i>
				
<p>February 26, 2016</p>	<p>February 6, 2015</p>	<p>August 4, 2014</p>	<p>May 29, 2013</p>	<p>April 19, 2013</p>
<p>Emergency Use of <i>In Vitro</i> Diagnostic Tests for Detection of Zika Virus and/or Diagnosis of Zika Virus Infection</p>	<p>Emergency Use of New <i>In Vitro</i> Diagnostics for Detection of Enterovirus D68</p>	<p>Emergency Use of <i>In Vitro</i> Diagnostics for Detection of Ebola Virus</p>	<p>Emergency Use of <i>In Vitro</i> Diagnostics for Detection of Middle East Respiratory Syndrome Coronavirus</p>	<p>Emergency Use of <i>In Vitro</i> Diagnostics for Detection of the Avian Influenza A (H7N9) Virus</p>

DMD EUA Program

DMD EUA PROGRAM

Proactive Outreach To Test Developers

Develop Relationships with Partners

Internal and Externally, Nationally and Internationally
BARDA, CDC, NIAID, DOD, WHO

Pre-EUA Submissions

Early engagement with firms – it is never too early to contact FDA

Draft EUA Review Template

Dynamic Review Team

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Partner Relationships Can.....



- Address:
 - Issues of sample availability
 - Issues of cross reactivity panels
 - In the case of Ebola - Overcome limited availability of BSL-3/4 testing facilities

Partner Relationships Can.....



- Address:
 - Issues of sample availability
 - Issues of cross reactivity panels
- } **BARDA Key Partner**
- In the case of Ebola - Overcome limited availability of BSL-3/4 testing facilities

Partner Relationships Can.....



- Facilitate:
 - Identification of firms with diagnostic products
 - Outreach
 - Understanding of diagnostic needs
 - Harmonization of assay requirements – WHO EUAL Listing and FDA EUA
 - Supply field data (WHO EUAL evaluation for diagnostics)
 - Mutual assistance with performance review/validation

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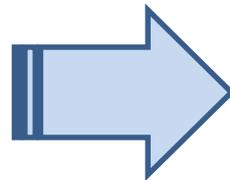
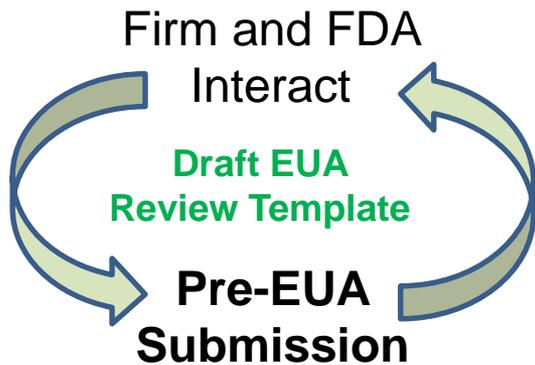
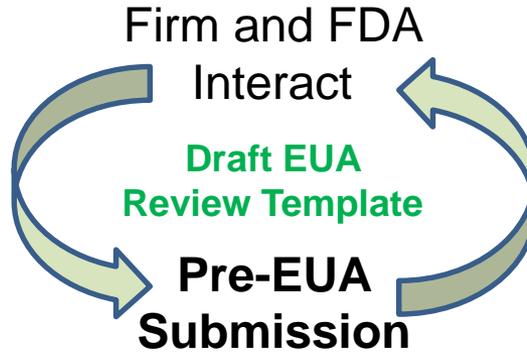
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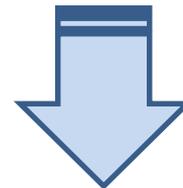
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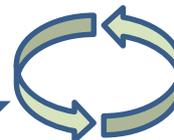
EUA Interactive Review



**EUA
Submission**



**Emergency
Use
Authorization**



Firm and FDA
Interact

DMD EUA Program

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Draft EUA Review Template

Dynamic Review Team

Draft EUA Review Template

- 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



Draft EUA Review Template

NAAT	Emergency Use Authorization (EUA)	De novo 510(k)
Limit of Detection (LoD)	Yes	Yes
Inclusivity	Yes <i>Some in silico</i>	Yes <i>Some in silico</i>
Exclusivity	Limited <i>Some in silico</i>	Extensive <i>Some in silico</i>
Interference	Situation specific	Yes
Precision	No	Yes - Multisite
Fresh Vs. Frozen	Fresh specimens preferred	Fresh specimens preferred
Specimen Stability	Preferred	Yes is needed
Clinical Evaluation	Limited – natural clinical specimens	Extensive – natural clinical specimens

Draft EUA Review Template

- **Dynamic Template:** Draft document, adapted depending on specific circumstances of the outbreak, Analyte & Technology (e.g., molecular, serology), starting point
- **Assist EUA Submitter and FDA Reviewers:**
 - Submitter fills out the template
 - Template serves as basis for interactive review
 - Template will later serve as sponsor's EUA Submission AND
 - Review memorandum for FDA

DMD EUA Program

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EUA Public Documents

TaqPath Zika Virus Kit (Thermo Fisher Scientific) ^

On August 2, 2017, the FDA issued an Emergency Use Authorization (EUA) for emergency use of Thermo Fisher Scientific's ("Thermo Fisher") TaqPath Zika Virus Kit (ZIKV) for the qualitative detection of RNA from Zika virus in human serum and urine (collected alongside a patient-matched serum specimen) from individuals meeting Centers for Disease Control and Prevention (CDC) Zika virus clinical criteria (e.g., clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated), by laboratories in the United States (U.S.) that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3). Test results are for the identification of Zika virus RNA. Zika virus RNA is generally detectable in serum during the acute phase of infection and, according to the updated CDC Guidance for U.S. Laboratories Testing for Zika Virus Infection, up to 14 days in serum and urine (possibly longer in urine), following onset of symptoms, if present. Positive results are indicative of current infection.

- [Letter of Authorization](#)
- [Fact Sheet for Healthcare Providers](#)
- [Fact Sheet for Patients](#)
- [Manufacturer Instructions/Package Insert](#)

LIAISON® XL Zika Capture IgM Assay (DiaSorin Incorporated) v

Gene-RADAR® Zika Virus Test (Nanobiosym Diagnostics, Inc.) v

Zika ELITe MGB® Kit U.S. (ELITechGroup Inc. Molecular Diagnostics) v

Abbott RealTime Zika (Abbott Molecular Inc.) v

Zika Virus Detection by RT-PCR Test (ARUP Laboratories) v

<http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika>

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

- [Letter of Authorization](#)
- [Fact Sheet for Healthcare Providers](#)
- [Fact Sheet for Patients](#)
- [Manufacturer Instructions/Package Insert](#)

Post EUA

FDA's role once an entity is issued an EUA:

- Follow up quickly with manufacturers if potential issues with performance are observed e.g., false positive or false negative results.
- Monitor supply and device usage as applicable.
- Effectively authorize modifications to EUA through Amendments (e.g., new specimen types, instruments).
- Follow up on reports of misuse of test and/or fraudulent claims

EUA Diagnostics

	H1N1	H7N9	MERS-CoV	Ebola	Enterovirus D68	Zika
EUA Declaration	April 26, 2009	April 19, 2013	May 29, 2013	August 4, 2014	February 6, 2015	February 26, 2016

Original EUA Diagnostics:

Molecular	17	2	2	9	1	15 [^]
Antigen	1	1	0	3* [^]	0	0
Serology	0	0	0	0	0	5
Total	18	3	2	12	1	20

EUA Re-authorizations and Amendment Granting's:

Total	10	1	2	24	0	30
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**Includes one product that was authorized for two different intended uses*

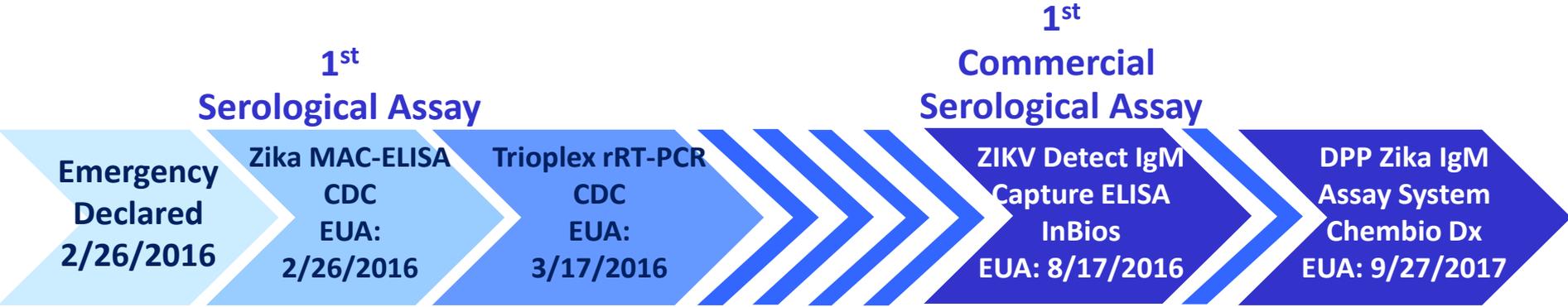
[^]Includes one product that was authorized but later withdrawn by the company



Common Challenges for EUA IVDs

- Evolving knowledge over the course of the emergency
- Lack of knowledge of the disease biology and natural course of infection, especially at beginning of emergency
- Uncertainty of best specimen type for molecular assays, especially at the beginning of emergency
- Availability of well-characterized specimens for assay development, testing and validation
- What is the best assay format, assay targets (target molecular sequence, antigens, what are important IgM epitopes, etc.)?

Zika EUAs



- **EUA Inquiries**
- **EUA Requests**
- **EUA issued, 1 withdrawn** (15 molecular, 5 IgM)

Challenges for Zika Virus IVDs

- Typically low viral load
- ~80% individuals are asymptomatic
- Short diagnostic window for molecular assays (< 14 days) = reliance on serological IgM assays
- Potential cross-reactivity of serological assays with other Flaviviruses – dengue, West Nile, yellow fever – problematic in South America and Puerto Rico
- PRNT follow-up testing
- Serological clinical specimens - **BARDA**



FDA Reference Materials

FDA Molecular Reference Material



- Two Zika Virus Strains – Asian Lineage*
 - S1 } Sensitivity Evaluation
 - S2 }
- Blinded Panel
- FDA Protocol

*Developed in collaboration with **CBER**

FDA Serological Reference Panel



- **Sensitivity Evaluation**
48 member panel (9 donors)
containing plasma from patients
initially PCR positive.*
- **Cross-reactivity Evaluation**
21 West Nile and 20 Dengue single
bleed specimens before 2016
outbreak.**

*Developed in collaborations with **Blood Systems Research Institute** (BSRI); National Heart, Lung, and Blood Institute (NHLBI) was the funding source that enabled the generation of the Zika panels; **Developed in collaboration with **CBER**

Evolving EUA



- **FDA Email boxes** developed and monitored to facilitate:
 - Initial interactions, request EUA Review Templates
 - CDRH-ZIKA-Templates@fda.hhs.gov
 - Report issues with EUA IVDs once in use
 - CDRH-EUA-Reporting@fda.hhs.gov
- **Tri-Agency Task Force for Emergency Diagnostics (TTFED)** – includes CDC, CMS and FDA:
 - Created to promote coordination among the 3 federal agencies to provide support for the implementation of IVD assays authorized under an Emergency Use Authorization (EUA)

After the Storm



EUA is not a substitute or short-cut for approval or clearance



- Development of 510k Requirements
- Outreach to Manufacturers:
 - Recommend pre-Submission (Q-Sub) in order to disseminate the 510k requirements without the need for a Guidance
 - Problem: Lack of Incentives - **BARDA**

FDA EUA IVD Resources



- **FDA Zika Response Updates Website**
 - <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm> (also available in Spanish and Portuguese)
- **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**
 - <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm> (April 2016)
- **FDA MCM Emergency Use Authorities Website** (*official updates*)
 - <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm411432.htm>
- **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

FDA EUA IVD Resources



For Zika molecular IVDs FDA developed tables summarizing the performance and key characteristics of each test

Table 1: Molecular Zika Virus (ZIKV) Emergency Use Authorization (EUA) Assays - Performance Characteristics

EUA Holder Assay Name*	Authorized Human Specimens [#]	ZIKV Gene Target(s)	ZIKV Limit of Detection ⁵ (Specimen)	Clinical Performance [^] (Specimen) [Rate] {95% CI}		FDA Reference Material Testing (RNA NAAT Detectable Units/mL)	
				Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)	S1	S2
Centers for Disease Control and Prevention (CDC) Trioplex Real-time RT-PCR Assay March 17, 2016	Serum (S) Whole blood (WB) Cerebrospinal fluid (CSF) Amniotic fluid (AF) Urine (U)	Envelope	(S) 19300 GCE/mL~ (U) 53800 GCE/mL~ (WB) 2430 GCE/mL	(S) 100.0% [19/19] {83.2-100%} (WB) 96.1% [146/152] {91.7-98.2%}	(S) 99.1% [110/111] {95.1-99.8%} (WB) 100.0% [116/116] {96.8-100%}	(S) 3300 (U) 1000	(S) 1670 (U) 1670
Quest Diagnostics Infectious Disease, Inc. Zika Virus RNA Qualitative Real-Time RT-PCR April 28, 2016	Serum Urine	Envelope and Membrane	(S) 250 copies/mL (U) 500 copies/mL	(S) 94.6% [53/56] {85.4-98.2%} (U) 100% [60/60] {94.0-100%}	(S) 100.0% [54/54] {93.4-100%} (U) 100% [59/59] {93.9-100%}	(S) 1000 (U) 1000	(S) 500 (U) 1500
altona Diagnostics GmbH RealStar Zika Virus RT-PCR Kit U.S.	Serum EDTA Plasma Urine	Proprietary	(S) 251.6 GEQ/mL (U) 79.6 GEQ/mL	(S) 96.8% [60/62] {89.0-99.1%} ^a	(S) 95.1% [39/41] {83.9-98.7%} ^a	(S) 3162 (U) 3162	(S) 5000 (U) 5000 Manual Ext

<https://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM606289.pdf>

FDA EUA IVD Resources



Table 2: Molecular Zika Virus (ZIKV) Emergency Use Authorization (EUA) Assays - Key Characteristics

EUA Holder Assay Name* (Date of Authorization)	Authorized Human Specimens (Volume) ⁵	RNA Extraction		Reaction Amplification Set-up		Approx. Turn Around Time per run	Approx. Through-put [^] per Instrument (Specimens per run)	Summary Characteristics
		Man.	Auto.	Man.	Auto.			
Centers for Disease Control and Prevention (CDC) Triplex Real-time RT-PCR Assay March 17, 2016	Serum Whole blood Cerebrospinal fluid Amniotic fluid Urine (140 – 1000 µL)	X	X	X		4 h	Low (24)	<ul style="list-style-type: none"> • First PCR assay to be granted an EUA • Triplex -Differentiation of ZIKV, DENV and CHIKV • 2 different instruments for PCR • 4 automated and 1 manual sample prep • Limited hand-on time for sample prep. and transfer to PCR cyclers; manual sample prep requires manual PCR set up as well. • Sample Input: 1.0 mL (automated); 0.14 mL (manual) • 5 sample types authorized: Serum, whole blood, CSF, amniotic fluid and urine
Quest Diagnostics Infectious Disease, Inc. Zika Virus RNA Qualitative Real-Time RT-PCR April 28, 2016	Serum Urine (500 µL)		X	X		5h	Low (30)	<ul style="list-style-type: none"> • Reference Laboratory • 1 instrument for PCR • 1 automated sample prep method • Limited hand-on time for sample prep. and transfer to PCR cyclers. • Sample Input: 0.5 mL • 1 sample type authorized: Serum
altona Diagnostics GmbH RealStar Zika Virus RT-PCR Kit U.S.	Serum EDTA Plasma							<ul style="list-style-type: none"> • 7 different instruments for PCR • 2 automated and 1 manual sample prep • Limited hand-on time for sample prep. and transfer to PCR cyclers; manual sample prep

<https://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM606290.pdf>

