

FDA Roles in Supporting the Emergency Use of Medical Countermeasures

NICBR-SIS 2018 Winter Forum

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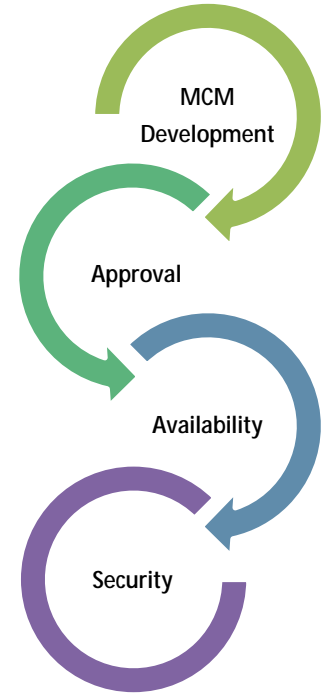
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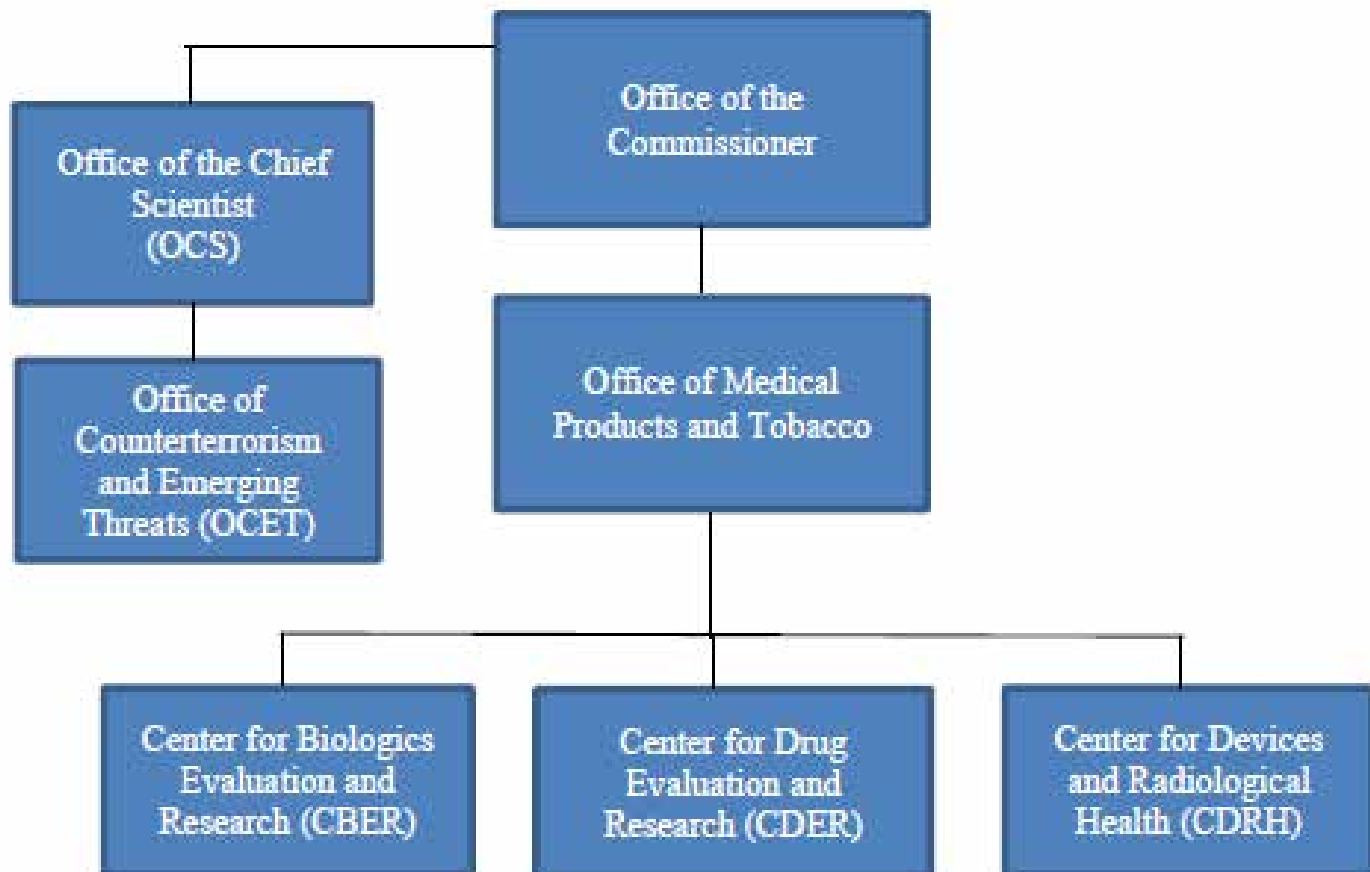
Counterterrorism and Emerging Threats



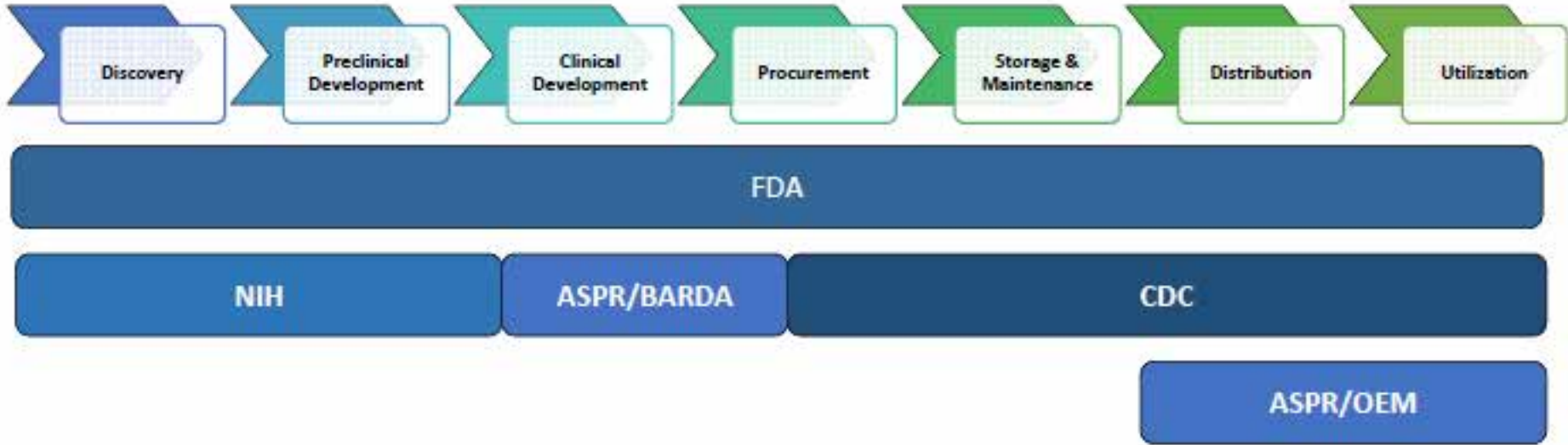
- Protecting the U.S. (civilians & warfighter) from threats
 - § Chemical, biological, radiological, nuclear (CBRN)
 - § Emerging infectious diseases
 - § Agents of war (warfighter)
- Ensuring medical countermeasures (MCMs) to counter these threats are safe, effective, and secure
 - § Drugs, biologics/vaccines, devices
- Office of Counterterrorism and Emerging Threats
 - § Coordinates FDA's Medical Countermeasures Initiative (MCMi) efforts closely with CBER, CDER, CDRH, and other FDA offices
 - § Facilitates development and availability of safe, effective MCMs (goal is product approval)
 - § Identifies/works to resolve complex scientific and regulatory challenges within FDA and with USG partners (including PHEMCE)
 - § Serves as point of entry on policy and planning for global health security, counterterrorism, emerging threats



Counterterrorism and Emerging Threats (very oversimplified org chart!)



Enterprise Approach



Sources of Federal Legal Preparedness Authorities for MCMs



- Public Health Service (PHS) Act (42 U.S.C. 201 et seq.); Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 201 et seq.)
- Public Health Threats and Emergencies Act (2000) (PL 106-505)
- Bioterrorism Act (2002) (PL 107-188)
- Smallpox Emergency Personnel Protection Act (2003) (PL 108-20)
- Project BioShield Act (2004) (PL 108-276)
- Public Readiness and Emergency Preparedness (PREP) Act (2005) (PL 109-148)
- Pandemic and All-Hazards Preparedness Act (PAHPA) (2006) (PL 109-417)
- Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) (2013) (PL 113-5)
- 21st Century Cures Act (Cures Act) (2016) (PL 114-255)
- PL 115-92 (H.R. 4374) (2017) (enacted with the National Defense Authorization Act (NDAA))

Why are legal/regulatory mechanisms for emergency use of MCMs needed?



- Without these mechanisms, certain preparedness and response activities at the local, state, and/or federal levels could otherwise violate provisions of the FD&C Act (e.g., render a product unapproved, adulterated, or misbranded):
 - Some MCMs needed for a response might not yet be approved, licensed, or cleared by FDA (e.g., Ebola, Zika, nerve agents)
 - Some MCMs needed for a response might be approved by FDA, but not for the emergency use (e.g., for a new indication)
 - Some MCMs might be approved for the emergency use, but:
 - Need to be dispensed without individual patient prescriptions (e.g., at points of dispensing (PODs)), by someone who is not a licensed health care professional, with streamlined instructions/fact sheets tailored for the emergency, and/or beyond the manufacturer-labeled expiration date
- Also, to ensure that available Public Readiness and Emergency Preparedness (PREP) Act protections apply (HHS)

FDA Authorities to Facilitate Access to MCMs in Response to Emergencies



- **Emergency Use Authorization (EUA)**
 - FD&C Act § 564
 - Established by Project BioShield Act (2004); amended by PAHPRA (2013), Cures Act (2016), and PL 115-92 (2017)
- **Other MCM emergency use authorities**
 - FD&C Act §§ 564A, 505-1, and 564B
 - Emergency dispensing orders, expiry dating extensions, waivers of CGMP and REMS requirements, and government stockpiling (FDA); emergency use instructions (EUI) (CDC)
 - Established by PAHPRA (2013); amended by Cures Act (2016)
- **Expanded access to investigational drugs and devices**
 - Investigational New Drug Application (IND) (21 CFR Parts 312.300-320)
 - Investigational Device Exemption (IDE) (21 CFR Part 812)

EUA Authority



- FD&C Act § 564
 - Established by Project BioShield Act (2004)
 - Amended by:
 - PAHPRA (2013) (to provide additional EUA flexibilities),
 - Cures Act (2016) (to add animal drugs), and
 - PL 115-92 (2017) (to provide additional EUA flexibilities and enhance engagements with DoD)
- With an EUA, FDA can authorize for use in emergencies involving a CBRN agent(s) (and, for DoD, an agent(s) of war):
 - The use of unapproved MCMs or
 - The unapproved use of approved MCMs (e.g., for a new indication)
- When scientific evidence is available to support MCM use in a CBRN emergency, issuing an EUA enables response stakeholders to use, or prepare to use, an MCM without violating the FD&C Act; also helps to ensure applicable PREP Act coverage

EUA Authority



- EUA requests are typically submitted by government partners (e.g., CDC, ASPR, DoD) or industry sponsors; FDA may prioritize requests if needed
- Overview of requirements/steps for EUA issuance:
 1. DHS, HHS, or DoD Secretary makes a specific type of **determination** (actual or potential emergency/threat):
 - DHS: Domestic emergency involving CBRN agent(s) or material threat determination (MTD),
 - HHS: Public health emergency involving CBRN agent(s), or
 - DoD: Military emergency involving a CBRN agent(s) or an agent(s) of war
 2. HHS Secretary issues a **declaration** that circumstances exist to justify EUA issuance based on 1 of the 4 types of determinations (*this is not a PHS Act § 319 Public Health Emergency declaration*)
 3. FDA ensures EUA **criteria for issuance** are met and issues the EUA when appropriate

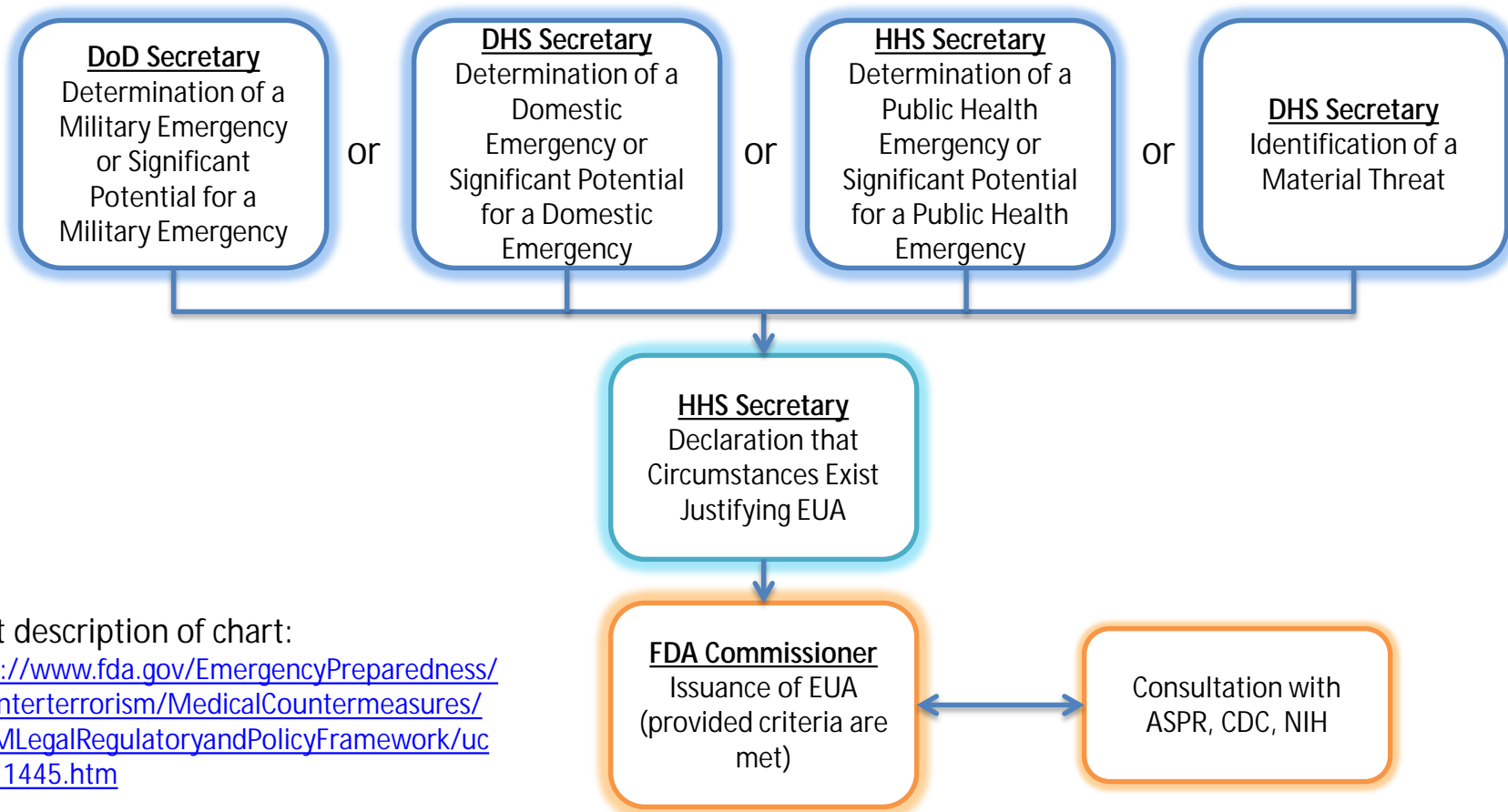
EUA Authority Amendment: PL 115-92



- Enacted December 12, 2017 (H.R. 4374)
- Amended section 564 of the FD&C Act to authorize additional emergency uses of medical products for threats (i.e., in addition to CBRN agents) to include “an agent or agents that may cause, or are otherwise associated with, an imminently life-threatening and specific risk to United States military forces”
- Also authorizes DoD to request, and FDA to provide, assistance to expedite development and review of products to diagnose, treat, or prevent serious or life-threatening diseases or conditions facing U.S. military forces
- January 16, 2018: FDA and DoD announced the launch of a joint program to prioritize the efficient development of safe and effective medical products intended for deployed U.S. military forces, including an “**Initial Work Plan for Products Relevant to DoD**”

Summary of EUA Process

- Enables FDA to authorize use of an unapproved medical product, or an unapproved use of an approved medical product, if certain criteria are met



Text description of chart:

<http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm411445.htm>

EUA Criteria for Issuance



- Criteria for issuance are based on the totality of scientific evidence available to FDA:
 - Serious or life-threatening illness/condition caused by the agent(s) referred to in the HHS Secretary’s EUA declaration
 - Reasonable belief the product “may be effective” in preventing, diagnosing, or treating serious or life-threatening diseases or conditions caused by the agent(s) (or mitigating a disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by the agent(s))
 - Known/potential benefits outweigh known/potential risks
 - No adequate, approved, and available alternative to the product



EUA Evidence of Effectiveness

- “May be effective”
- Provides for a lower level of evidence than the "effectiveness" standard FDA uses for product approvals
- FDA intends to assess the potential effectiveness of a possible EUA product on a case-by-case basis using a risk-benefit analysis (next slide)
- If, based on the totality of the scientific evidence available, it is reasonable to believe that the product may be effective for the specified use, FDA may authorize its emergency use, provided that other statutory criteria for issuing an EUA also are met
- The amount, type, and quality of evidence available to support an EUA may not always be the same as that required for expanded access, IDEs, or humanitarian device exemptions under the FD&C Act and FDA regulations



EUA Risk/Benefit Analysis

- FDA must take into consideration the material threat posed by the agent(s) identified in the HHS Secretary's EUA declaration if applicable (section 564(c))
- In determining whether the known and potential benefits of the product outweigh the known and potential risks, FDA intends to look at the totality of the scientific evidence to make an overall risk-benefit determination
 - Such evidence could arise from a variety of sources and may include (but is not limited to): results of domestic and foreign clinical trials, *in vivo* efficacy data from animal models, and *in vitro* data
- FDA will also assess the quality and quantity of the available evidence, given the current state of scientific knowledge
- The types of evidence that FDA may consider and that should be submitted to support a request for an EUA are discussed in section III.D.2 of the EUA guidance



EUA Conditions of Authorization

- Safeguards included in, and specific to, each EUA. Some are required, while some are discretionary to protect the public health. For example:
 - Information on emergency use (e.g., fact sheets for product recipients and for health care professionals)
 - e.g.) Notification that the product is being used under an EUA and is not FDA-approved
 - Dispensing/screening procedures
 - Record keeping and monitoring of adverse events
 - Collection of information
 - Roles (e.g., for DoD, health care professionals, laboratories, etc.)
 - Advertising and promotion



EUA Package

- Consists of:
 - A letter of authorization and
 - Any accompanying materials (e.g., fact sheets for health care professionals, fact sheets for patients/recipients, instructions for use, labels)
- Made available publicly on the FDA website and in the *Federal Register*
 - <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>
- May be amended

Amending and Terminating/Revoking EUAs



- Amendment
 - An EUA may be amended after issuance (e.g., to allow for a new strength of the authorized product, use in a new patient population, etc.)
 - In some cases, the entire EUA might be reissued
 - In other cases, if the letter of authorization delegates authority for certain actions, a “letter granting EUA amendment” may be issued without reissuing the entire EUA
- Termination or Revocation
 - An EUA will terminate upon termination of the HHS Secretary’s supporting EUA declaration (i.e., if the emergency/threat circumstances no longer exist or there is a change in the approval status of the product)
 - FDA may revoke an EUA if the emergency/threat circumstances no longer exist, the criteria for issuance are no longer met, or to protect the public health or safety

Example of EUA Issuance Process: Rafa Atropine Auto-Injector



- March 9, 2017: CDC requested an EUA for the 2 mg Atropine Auto-Injector manufactured by Rafa Laboratories Ltd. for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents (NA) or certain insecticides (organophosphorus and/or carbamate)
- April 11, 2017:
 - HHS Secretary **determined** under section 564 of the FD&C Act that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves **nerve agents or certain insecticides (organophosphorus and/or carbamate)**
 - Based on the above determination, the HHS Secretary **declared** under section 564 that circumstances exist justifying the authorization of the emergency use of **injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning**, subject to the terms of any EUA issued
 - This declaration is not limited to the Rafa product; it was drafted to be flexible in anticipation of possible additional EUAs for other injectable NA treatments

Example of EUA Issuance Process: Rafa Atropine Auto-Injector (cont.)



- April 11, 2017: FDA issued an **EUA** for the Rafa Atropine Auto-Injector (2 mg) (this is the 1st EUA for a nerve agent product)
- May 4, 2017: HHS Secretary issued a **PREP Act Declaration** to provide liability protections for MCMs against nerve agents and certain insecticides (the effective date is April 11, the date of issuance of the Rafa EUA)
- May 23, 2017: Per CDC request and FDA review of data, FDA issued a **Letter Granting EUA Amendment** to authorize (1) use of 0.5 mg and 1 mg (i.e., pediatric) strengths and (2) revised fact sheets under the April 11 Rafa EUA
- Rafa EUA, Letter Granting EUA Amendment, HHS Nerve Agent Determination/Declaration, and PREP Act Declaration are available at:
 - <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm#nerveagents>



List of EUAs Issued

EUAs Issued by FDA			
Year	MCM	Requester	Status
Anthrax (<i>Bacillus anthracis</i>)			
2005	Anthrax Vaccine Adsorbed (AVA)	DoD	Terminated
2008 (<i>reissued 2009, 2010, 2011</i>)	Doxycycline hyclate 100 mg oral tablets (in National Postal Model home/workplace kits)	HHS (ASPR/BARDA)	Current (2011 version)
2011	Doxycycline (oral forms) for mass dispensing	HHS (CDC)	Current*
H1N1 Influenza Pandemic (2009)			
2009-2010	Antivirals (3)	HHS (CDC)	Terminated (all H1N1 EUAs)
	IVDs (18)	Various	
	Disposable N95 respirators	HHS (CDC)	
H7N9 Influenza			
2013	CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay	HHS (CDC)	Current
2014	Lyra Influenza A Subtype H7N9 Assay	Quidel Corp.	Current
2014	A/H7N9 Influenza Rapid Test	Arbor Vita Corp.	Current
Middle East Respiratory Syndrome Coronavirus (MERS-CoV)			
2013 (<i>reissued 2014</i>)	CDC Novel Coronavirus 2012 Real-time RT-PCR Assay	HHS (CDC)	Current
2015 (<i>reissued 2016</i>)	RealStar MERS-CoV RT-PCR Kit U.S.	altona Diag. GmbH	Current

* To be terminated due to April 2016 issuance of doxycycline emergency dispensing order, CGMP waiver, and CDC EUI (under sec. 564A of the FD&C Act).



Updated August 21, 2017

EUAs Issued by FDA

Year	MCM	Requester	Status
Ebola Virus			
2014 (<i>reissued 2014</i>)	DoD EZ1 Real-time RT-PCR Assay	DoD	Current
2014 (<i>reissued 2015</i>)	CDC Ebola VP40 rRT-PCR Assay	HHS (CDC)	Current
2014 (<i>reissued 2015</i>)	CDC Ebola NP rRT-PCR Assay	HHS (CDC)	Current
2014 (<i>reissued 2015</i>)	FilmArray NGDS BT-E Assay	BioFire Defense, LLC	Current
2014 (<i>reissued 2015</i>)	FilmArray Biothreat-E test	BioFire Defense, LLC	Current
2014 (<i>reissued 2014</i>)	RealStar Ebolavirus RT-PCR Kit 1.0	altona Diag. GmbH	Current
2014	LightMix Ebola Zaire rRT-PCR Test	Roche Molecular Systems, Inc.	Current
2015 (<i>reissued 2016</i>)	ReEBOV Antigen Rapid Test	Zalgen Labs, LLC	Current
2015	Xpert Ebola Assay	Cepheid	Current
2015	OraQuick Ebola Rapid Antigen Test (use with whole blood)	OraSure Technologies, Inc.	Current
2016 (<i>reissued 2016</i>)	OraQuick Ebola Rapid Antigen Test (use with cadaveric oral fluid)	OraSure Technologies, Inc.	Current
2016	Idylla Ebola Virus Triage Test	Biocartis NV	Current
Enterovirus D68 (EV-D68)			
2015	CDC EV-D68 2014 rRT-PCR Assay	HHS (CDC)	Current
Nerve Agents			
2017 (<i>amended 2017**</i>)	2 mg Atropine Auto-Injector	CDC	Current

** In response to CDC's request, on May 23, 2017, FDA issued an EUA amendment to (1) authorize additional strengths (i.e., 0.5 mg and 1 mg) of the authorized Rafa Atropine Auto-Injector under the April 11, 2017, EUA and (2) update the authorized EUA Fact Sheets for the authorized Rafa Atropine Auto-Injector to include information about the 0.5 mg and 1 mg strengths. The additional strengths are for pediatric patients weighing 15-40 pounds (0.5 mg) and 41-90 pounds (1.0 mg). The 2 mg strength remains authorized under the EUA for adults and children weighing over 90 pounds.

EUAs Issued by FDA

Year	MCM	Requester	Status
Zika Virus			
2016 (<i>amended 2016 & 2017</i>)	CDC Zika MAC-ELISA (IgM)	HHS (CDC)	Current
2016 (<i>amended 2016 & 2017</i>)	CDC Triplex Real-time RT-PCR Assay	HHS (CDC)	Current
2016 (<i>amended 2016 & 2017</i>)	Zika Virus RNA Qualitative Real-Time RT-PCR	Quest Diagnostics Infectious Disease, Inc.	Current
2016 (<i>amended 2016 & 2017</i>)	RealStar Zika Virus RT-PCR Kit U.S.	altona Diagnostics GmbH	Current
2016 (<i>amended 2016 & 2017</i>)	Aptima Zika Virus assay	Hologic, Inc.	Current
2016 (<i>amended 2017</i>)	Zika Virus Real-time RT-PCR Test	Viracor Eurofins	Current
2016 (<i>amended 2016</i>)	VERSANT® Zika RNA 1.0 Assay (kPCR) Kit	Siemens Healthcare Diagnostics Inc.	Current
2016 (<i>amended 2016</i>)	LightMix® Zika rRT-PCR Test	Roche Molecular Systems, Inc.	Revoked (2017)
2016 (<i>amended 2017</i>)	xMAP® MultiFLEX™ Zika RNA Assay	Luminex Corporation	Current
2016 (<i>amended 2017</i>)	ZIKV Detect™ IgM Capture ELISA	InBios International, Inc.	Current
2016	Sentosa® SA ZIKV RT-PCR Test	Vela Diagnostics USA, Inc.	Current
2016	Zika Virus Detection by RT - PCR Test	ARUP Laboratories	Current
2016 (<i>amended 2017</i>)	Abbott RealTime ZIKA	Abbott Molecular Inc.	Current
2016	Zika ELITe MGB® Kit U.S.	ELITechGroup Inc. Molecular Diagnostics	Current
2017	Gene-RADAR® Zika Virus Test	Nanobiosym Diagnostics, Inc.	Current
2017	LIAISON® XL Zika Capture IgM Assay	DiaSorin Incorporated	Current
2017	TaqPath Zika Virus Kit (ZIKV)	Thermo Fisher Scientific	Current
2017	CII-ArboViroPlex rRT-PCR	Columbia University	Current

EUAs Issued by FDA

Year	MCM	Requester	Status
Zika Virus (cont.)			
2017	ADVIA Centaur Zika test	Siemens Healthcare Diagnostics Inc.	Current
2017	DPP Zika IgM Assay System	Chembio Diagnostic Systems, Inc.	Current

Other MCM Emergency Use Authorities



- Established by PAHPRA (2013); amended by 21st Century Cures Act (2016)
- For MCMs that are FDA-approved/cleared for CBRN use, to facilitate stakeholder preparedness and response without EUA issuance, thereby preserving applicable PREP Act protections (FD&C Act § 564A)
 - Emergency dispensing orders (FDA)
 - Emergency use instructions (EUI) (CDC)
 - Expiration dating extensions (FDA)
 - Current Good Manufacturing Practices (CGMP) waivers (FDA)
 - Risk Evaluation and Mitigation Strategy (REMS) waivers (FDA)
- Pre-positioning (FD&C Act § 564B)
 - PAHPRA allows pre-positioning of approved/unapproved MCMs by or on behalf of government entities (federal, state, local) in anticipation of FDA approval, clearance, licensure or EUA or IND issuance
 - But, the MCM may not be used until it is approved or authorized for emergency or investigational use



Looking Ahead...

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
- **Final Guidance on EUAs & Other MCM Emergency Use Authorities**
 - <https://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM493627.pdf> (January 2017)
- **MCM Emergency Use Authorities Website**
 - <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm411432.htm>
- **FDA Zika Response Updates Website**
 - <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm>
- **PL 115-92 (H.R. 4374) (including Initial Work Plan issued on January 16, 2018)**
 - <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm2007271.htm#PL11592>
- **21st Century Cures Act: MCM-Related Provisions (including MCM PRVs)**
 - <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm566498.htm>
- **PREP Act (HHS)**
 - <http://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx>

Thank you!



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