U.S. FOOD & DRUG ADMINISTRATION

Emergency Use of Medical Countermeasures:
FDA Roles and Authorities

University of Arizona
Regulatory Science Series

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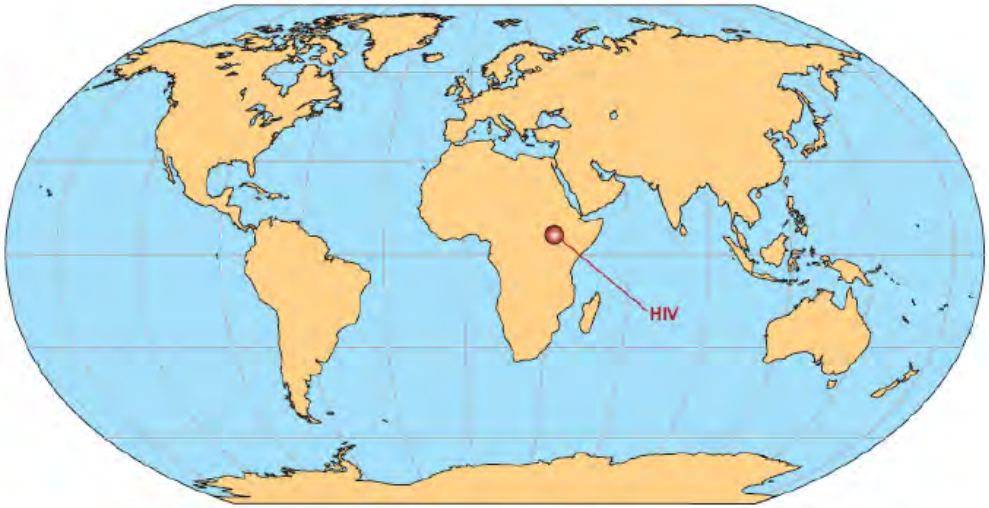
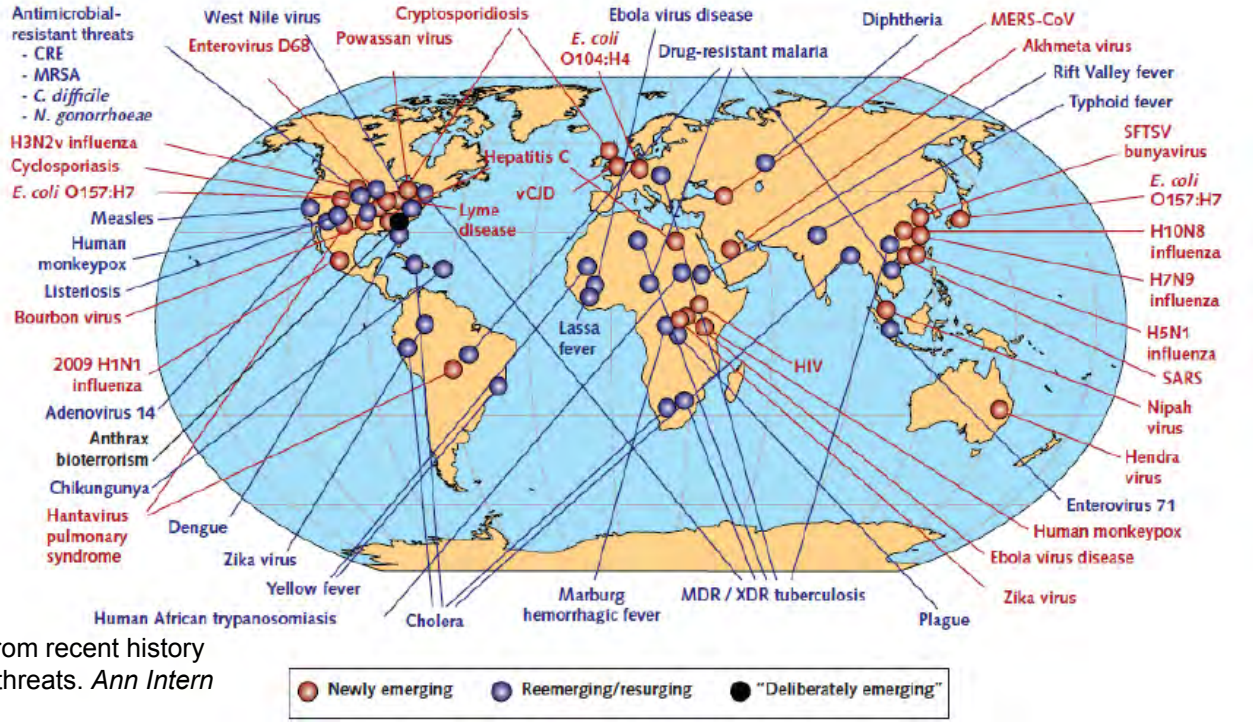
Office of the Commissioner

Examples of Evolving Threat Space

Early 1980's...



...Accumulation of emerging/reemerging infectious diseases



Source: Paules CI, et al. Lessons from recent history about emerging infectious disease threats. *Ann Intern Med.* 2017;167(11):805-811.

Overview of Public Health Legal Preparedness

Public Health Legal Preparedness

- Term first appeared in late 1990s; subset of public health preparedness
- Recognizes the essential role law plays in protecting the public from catastrophic health events
  - Core foundation to ensure U.S. is prepared to prevent, respond to, and reduce adverse effects of public health emergencies
- May impact a range of players during disasters
  - e.g.) health officials, hospitals, health care practitioners, first responders, businesses, medical countermeasure (MCM) manufacturers, public, etc.

Source: Moulton et al. *Journal of Law, Medicine & Ethics*. 2003;31; The National Action Agenda for Public Health Legal Preparedness. *Journal of Law, Medicine & Ethics*. 2008;36(1).

Levels (and Layers) of Authority

- Global
  - WHO (Director-General) (e.g., IHR, PHEIC declaration)
  - Individual countries (substantial variation in laws, capabilities, declarations)
- Federal (e.g., President, Cabinet Secretaries)
  - e.g.) emergency laws, declarations
- State (e.g., Governor, Secretary of Health)
  - e.g.) traditional public health powers (police powers), emergency laws and declarations (much variation)
- Local (e.g., Mayor, County Executive, Health Officer)

Examples of Legal Preparedness/ Response Tools

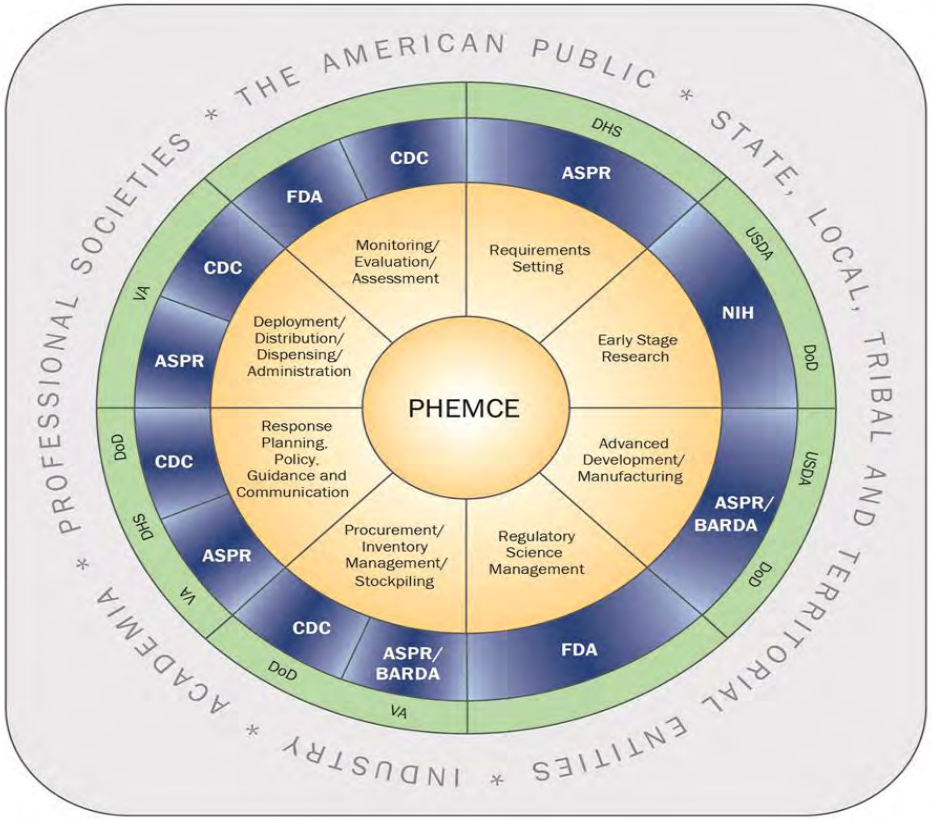
- Declarations
- Executive orders
- Isolation and quarantine authorities (federal and state)
- Volunteer and other liability protections
- 1135 waivers
- Mutual aid agreements—Emergency Management Assistance Compact (EMAC)
- Emergency use authorities for MCMs

FDA Roles

Counterterrorism and Emerging Threats

- Protecting the U.S. (civilians & the warfighter) from threats
  - Chemical, biological, radiological, and 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
- FDA Office of Counterterrorism and Emerging Threats
  - Coordinates FDA's Medical Countermeasures Initiative (MCMi) efforts closely with CBER, CDER, CDRH, and other FDA centers and 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

Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)



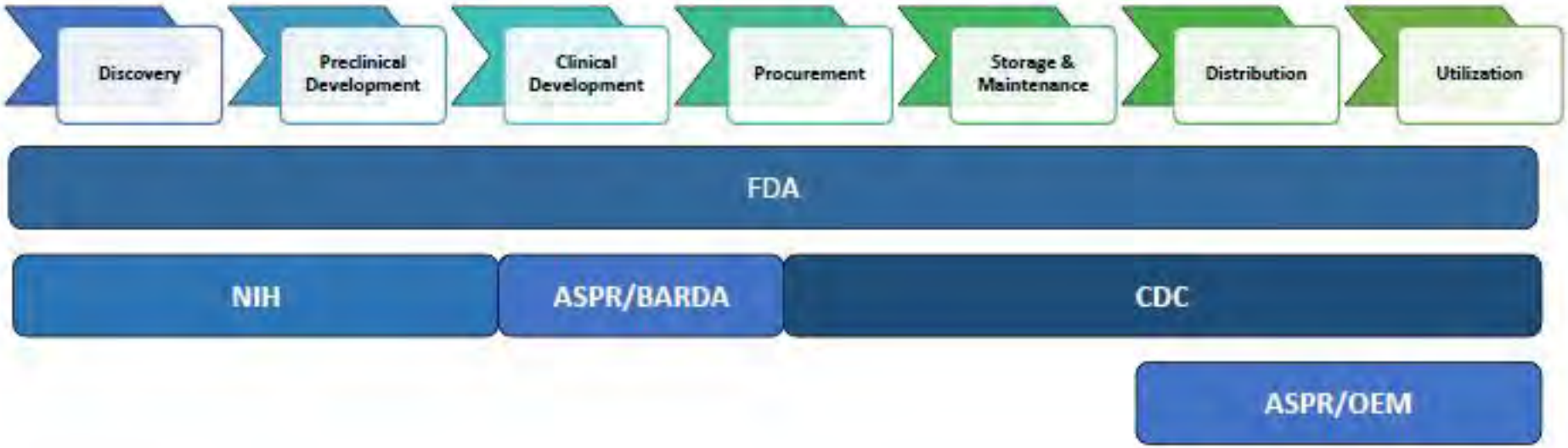
Key

- PHEMCE Mission Components
- HHS PHEMCE Agencies
- Non-HHS PHEMCE Agencies
- Non-Federal Stakeholders

Acronyms

PHEMCE: Public Health Emergency Medical Countermeasures Enterprise
DHS: Department of Homeland Security
DoD: Department of Defense
USDA: U.S. Department of Agriculture
VA: Department of Veterans Affairs
HHS: Department of Health and Human Services
ASPR: Assistant Secretary for Preparedness and Response
BARDA: Biomedical Advanced Research & Development Authority
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
NIH: National Institutes of Health

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 a specific 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 HHS Public Readiness and Emergency Preparedness (PREP) Act protections apply

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 Current Good Manufacturing Practice (CGMP) and Risk Evaluation and Mitigation Strategy (REMS) requirements, and government stockpiling (FDA); emergency use instructions (EUI) (delegated to 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

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 FDA-Department of Defense (DoD) engagements)
- 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; an EUA can also help to ensure applicable PREP Act coverage is available

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**"

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. Secretary of Department of Homeland Security (DHS), Health and Human Services (HHS), or DoD makes a specific type of **determination** (actual or potential emergency/threat):

   - DHS: Domestic emergency involving CBRN agent(s) or material threat determination (MTD),

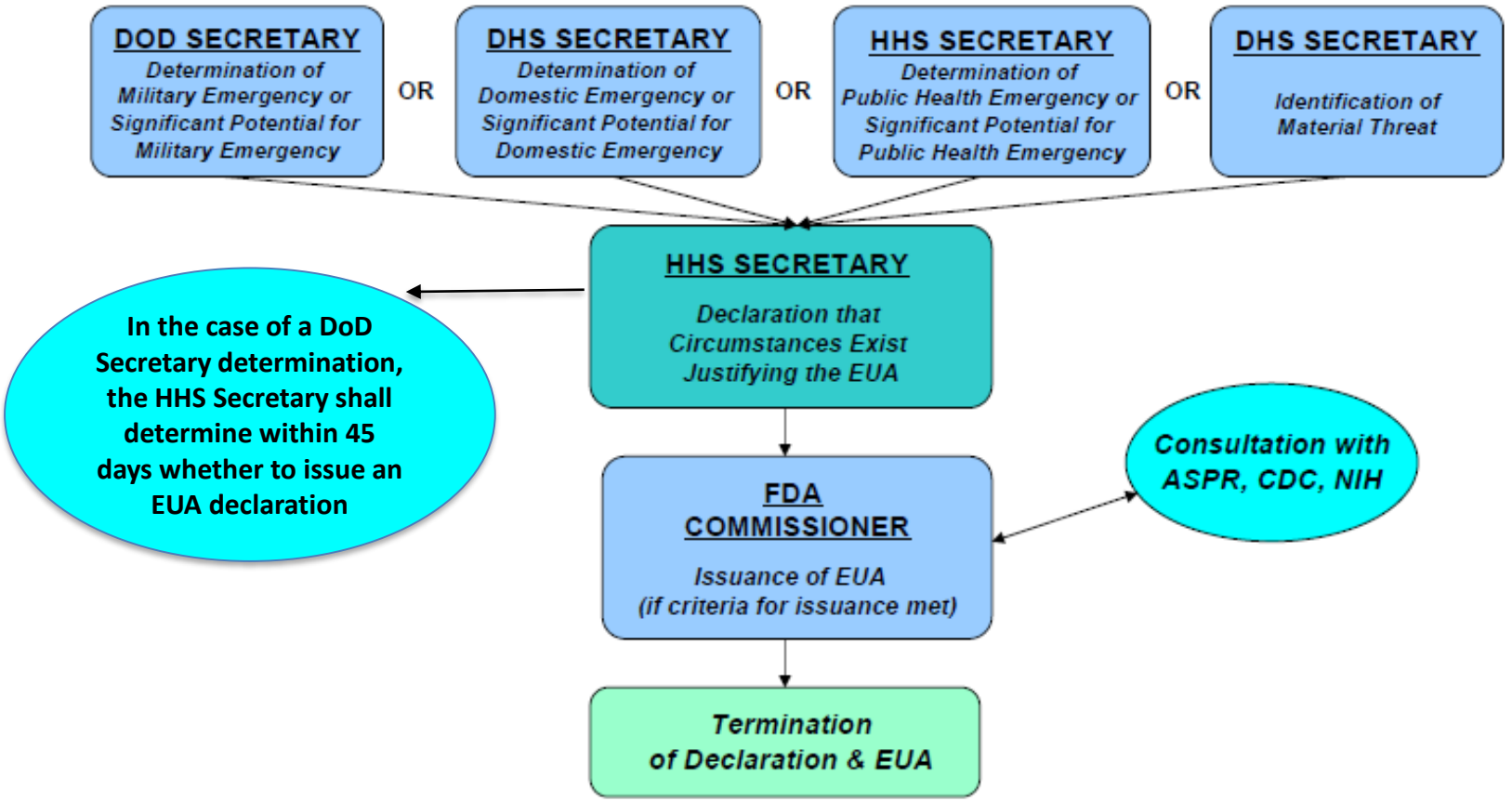
   - HHS: Public health emergency involving CBRN agent(s), or

   - DoD: Military emergency involving a CBRN agent(s) or an agent(s) of war

2. HHS Secretary issues a **declaration** ("EUA declaration") that circumstances exist to justify EUA issuance based on 1 of the 4 types of determinations listed above (*this is not a PHS Act § 319 Public Health Emergency (PHE) declaration*)

3. FDA ensures EUA **criteria for issuance** are met and issues the EUA when appropriate

Summary of Process for EUA Issuance



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

- An 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

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 same date of issuance of as 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) use of revised fact sheets
- January 24, 2018: Per CDC request and FDA review of data, FDA issued another **Letter Granting EUA Amendment** to authorize (1) administration through clothing and (2) certain manufacturing changes
- Rafa EUA, Letters 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

FACT SHEET FOR PATIENTS AND CAREGIVERS:
Use of the Rafa Atropine Auto-Injector for Initial Treatment of Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning

You are being given the Rafa Atropine Auto-Injector because you or someone you know may have been exposed to nerve agents or certain insecticides (organophosphorus and/or carbamate) that could cause injury, harm, or death. These nerve agents or insecticides attack the central nervous system, the part of your body that controls your brain, spinal cord, and nerves. These nerve agents or insecticides can be a liquid, gas, or solid. As little as one drop of some nerve agents on your skin can cause death within 15 minutes of contact.

Atropine is used as the initial treatment for symptoms of nerve agent or certain insecticide poisoning. The Rafa Atropine Auto-Injector, which contains atropine, is being made available to treat poisoning by nerve agents or certain insecticides (organophosphorus and/or carbamate). This medicine may increase your chance of survival after coming in contact with these nerve agents or certain insecticides.

This Fact Sheet contains:

A. Information to help you understand the risks and benefits of the Rafa Atropine Auto-Injector you have received or may receive.

B. Instructions on how you or a caregiver can give (administer) the Rafa Atropine Auto-Injector in an emergency if a healthcare provider is not available to administer it.

A. INFORMATION ABOUT THE RISKS AND BENEFITS OF THE RAFA ATROPINE AUTO-INJECTOR

What is atropine and what is the Rafa Atropine Auto-Injector?

Atropine is a medicine to help reduce or block the effects of nerve agent or certain insecticide poisoning (organophosphorus and/or carbamate). This medicine comes in a self-containing device (auto-injector) which gives only a single dose by injection (shot) into the outer thigh. The needle that springs out of the device to deliver a single dose cannot be drawn back and the device cannot be reused. Each injector called the Rafa Atropine Auto-Injector is made to self-administer or administer the medicine to another person. The Rafa Atropine Auto-Injector is available in three doses that are administered based on a person's weight or age: 0.5 mg, 1 mg, or 2 mg. The different auto-injector doses are color-coded, as shown below. **See Table 1 for selecting the correct dose based on a person's weight (or age if the weight is not known).**

0.5 mg Atropine Auto-Injector (Blue label)	1 mg Atropine Auto-Injector (Red label)	2 mg Atropine Auto-Injector (Green label)

Who can receive the Rafa Atropine Auto-Injector?

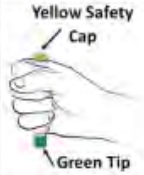
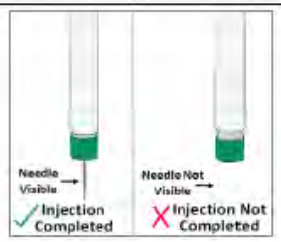
The Rafa Atropine Auto-Injector should be administered only to adults and children weighing 15 lbs [7 kg] or more (generally 6 months of age and older) who have been exposed to nerve agents or certain insecticides and are experiencing symptoms of nerve agent or insecticide poisoning. **See Table 2 below for symptoms of nerve agent or insecticide poisoning.**

What are the symptoms of nerve agent or insecticide poisoning?

Symptoms of nerve agent or insecticide poisoning may include nausea, vomiting, stomach cramps, inability to control urine and/or stool, confusion, muscle twitching or weakness, and convulsions (seizures). The number of Rafa Atropine Auto-Injectors needed depends on how **mild or severe the symptoms are. See Table 2 below for mild or severe symptoms of nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning.**

https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm#nerveagents

Figure 2. Instructions on how to administer Rafa Atropine Auto-Injector to yourself or others

	A.) Confirm you have the correct dose based on weight or age (see **Table 1**). Hold the plastic sleeve on both sides of the perforation and tear apart at edge to open. Remove the auto-injector from the plastic sleeve. **Be careful not to place fingers on the green tip.**
	B.) Firmly hold the auto-injector with the green tip pointed down.
	C.) Pull off the yellow safety cap with your other hand.
	D.) Aim and firmly jab the green tip straight down (a 90° angle) against the outer thigh. The auto-injector device will give the medicine when you do this. **You can inject through clothing, but make sure pockets at the injection site are empty.** *Infants, small children, and adults who may not have a lot of fat at the injection site should also be injected in the thigh, but before giving the injection, bunch up the thigh to provide a thicker area of injection.
	E.) Hold the auto-injector firmly in place for at least 10 seconds to allow the injection to finish.
	F.) After 10 seconds, remove the auto-injector from the thigh (or from the thigh of the individual to whom you are administering the auto-injector) and massage the injection site in a circle motion for several seconds. **Note: If you do not see the needle visible after removal from the thigh it means an injection did not occur. Check to be sure the yellow safety cap has been removed. After yellow safety cap removal has been verified, repeat steps D and E pressing harder against the thigh to activate the injector. If you still do not see the needle, use a new auto-injector and start over again at step A.**

https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm#nerveagents

List of EUAs Issued

EUAs Issued by FDA

Year	MCM	Requester	Status
Anthrax (*Bacillus anthracis*)			
2005	Anthrax Vaccine Adsorbed (AVA)	DoD	Terminated
2008 (*reissued 2009, 2010, 2011*)	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 (*reissued 2014*)	CDC Novel Coronavirus 2012 Real-time RT-PCR Assay	HHS (CDC)	Current
2015 (*reissued 2016*)	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).
- For the most current FDA EUA information, see: www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

Updated August 21, 2017

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF THE COMMISSIONER
MEDICAL COUNTERMEASURES INITIATIVE

EUAs Issued by FDA			
Year	**MCM**	**Requester**	**Status**
Ebola Virus			
2014 (*reissued 2014*)	DoD EZ1 Real-time RT-PCR Assay	DoD	Current
2014 (*reissued 2015*)	CDC Ebola VP40 rRT-PCR Assay	HHS (CDC)	Current
2014 (*reissued 2015*)	CDC Ebola NP rRT-PCR Assay	HHS (CDC)	Current
2014 (*reissued 2015*)	FilmArray NGDS BT-E Assay	BioFire Defense, LLC	Current
2014 (reissued 2015)	FilmArray Biothreat-E test	BioFire Defense, LLC	Current
2014 (*reissued 2014*)	RealStar Ebolavirus RT-PCR Kit 1.0	altona Diag. GmbH	Current
2014	LightMix Ebola Zaire rRT-PCR Test	Roche Molecular Systems, Inc.	Current
2015 (*reissued 2016*)	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 *(reissued 2016)*	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 *(amended 2017, 2018**)*	2 mg Atropine Auto-Injector	CDC	Current

** On May 23, 2017, at CDC's request, FDA issued an EUA amendment to authorize (1) use of pediatric strengths (i.e., 0.5 mg and 1 mg) of the Rafa Atropine Auto-Injector, in addition to the 2 mg strength, and (2) updates to the original fact sheets to include all three strengths. On January 24, 2018, at CDC's request, FDA issued an EUA amendment to authorize (1) administration through clothing and (2) certain manufacturing changes.

Updated January 24, 2018

EUAs Issued by FDA

Year	MCM	Requester	Status
Zika Virus			
2016 *(amended 2016 & 2017)*	*CDC Zika MAC-ELISA (IgM)*	HHS (CDC)	Current
2016 *(amended 2016 & 2017)*	*CDC Trioplex Real-time RT-PCR Assay*	HHS (CDC)	Current
2016 *(amended 2016 & 2017)*	Zika Virus RNA Qualitative Real-Time RT-PCR	Quest Diagnostics Infectious Disease, Inc.	Current
2016 *(amended 2016 & 2017)*	RealStar Zika Virus RT-PCR Kit U.S.	altona Diagnostics GmbH	Current
2016 *(amended 2016 & 2017)*	Aptima Zika Virus assay	Hologic, Inc.	Current
2016 *(amended 2017)*	Zika Virus Real-time RT-PCR Test	Viracor Eurofins	Current
2016 *(amended 2016)*	VERSANT® Zika RNA 1.0 Assay (kPCR) Kit	Siemens Healthcare Diagnostics Inc.	Current
2016 *(amended 2016)*	LightMix® Zika rRT-PCR Test	Roche Molecular Systems, Inc.	Revoked *(2017)*
2016 *(amended 2017)*	xMAP® MultiFLEX™ Zika RNA Assay	Luminex Corporation	Current
2016 *(amended 2017)*	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 *(amended 2017)*	Abbott RealTi*m*e 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

Updated August 21, 2017

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

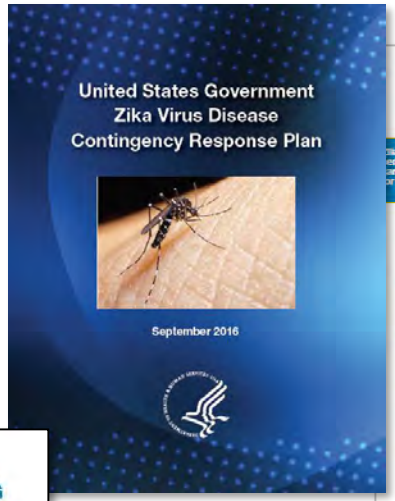
Updated September 27, 2017

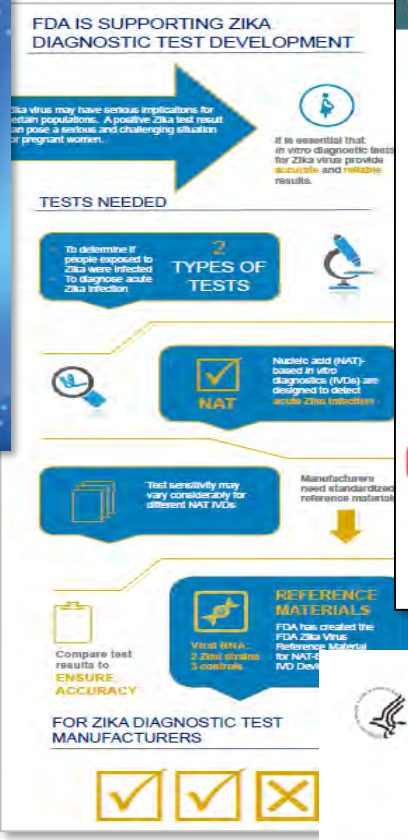
Other MCM Emergency Use Authorities

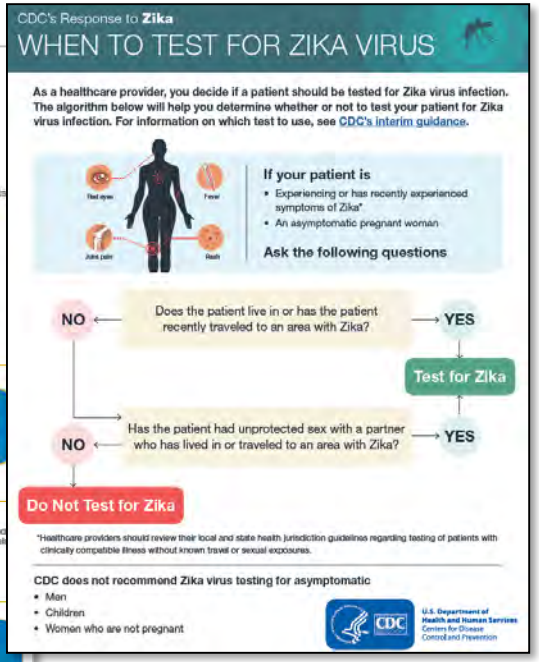
Other MCM Emergency Use Authorities

- 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, while preserving applicable PREP Act protections (FD&C Act § 564A)
  - Emergency dispensing orders (FDA)
  - Emergency use instructions (EUI) (CDC)
  - Expiration dating extensions (FDA)
  - CGMP waivers (FDA)
  - REMS waivers (FDA)
- Pre-positioning (FD&C Act § 564B)
  - PAHPRA allows for 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

Overview of FDA Zika Virus Response







FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Releases Final Environmental Assessment for Genetically Engineered Mosquito

Update

August 5, 2016

The FDA has completed the environmental review for a proposed field trial to determine whether the release of Oxitec Ltd.'s genetically engineered (GE) mosquitoes (OX513A) will suppress the local *Aedes aegypti* mosquito population in the release area at Key Haven, Florida. After considering thousands of public comments, the FDA has published a final environmental assessment (EA) and finding of no significant impact (FONSI) that agrees with the EA's conclusion that the proposed field trial will not have significant impacts on the environment.

Revised Recommendations for Reduci the Risk of Zika Virus Transmission b Blood and Blood Components

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

Considerations for Developing a Zika Virus Vaccine

Hilary D. Marston, M.D., M.P.H., Nicole Lurie, M.D., M.S.P.H, Luciana L. Borio, M.D., and Anthony S. Fauci, M.D.

The rapid spread of Zika virus through the Americas and its devastating consequences for pregnant women and infants have precipitated an international, multisectoral response.

nation averts congenital anomalies will most likely require postlicensure studies.

Prevention of congenital anomalies through vaccination of women

FDA U.S. FOOD & DRUG ADMINISTRATION

Office of Medical Device and Radiological Health Operations (OMDRHO)
Division 2 Central
555 Winderley Pl # 200
Maitland, FL 32751
Telephone: (407) 475-4700

WARNING LETTER
CMS# 526232

UNITED PARCEL SERVICE
w/DELIVERY CONFIRMATION

December 7, 2017

Jack L. Aronowitz, President
Health-Chem Diagnostics, LLC
Division of P & L Development, LLC
3341 SW 15th Street
Pompano Beach, FL 33069

Dear Mr. Aronowitz:

During an inspection of your firm, Health-Chem Diagnostics, LLC, located in Pompano Beach, Florida,on January 2, 2017, through February 3, 2017, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures in vitro diagnostic tests including, but not limited to, tests for pregnancy and Zika virus. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body.

In addition, the inspection also revealed your One-Step Test for Zika Virus Antibody and One-Step Test for Zika Virus IgG/IgM Antibody tests are adulterated under section 501(f)(1)(B) of the Act, 21 U.S.C. § 351(f)(1)(B), because your firm does not have an approved application for premarket

www.fda.gov

FDA Zika Virus Response

- FDA has been fully engaged with USG and other partners in responding to the Zika virus outbreak
- No FDA-approved, -licensed, or -cleared vaccines, treatments, or diagnostic tests to prevent, treat, or diagnose Zika virus available
- One FDA-approved test for screening Zika virus in blood donations
  - Intended for use by blood collection establishments to detect Zika virus in blood donations, not for individual diagnosis of Zika virus infection (October 2017)
- Prepared to leverage our authorities to help accelerate the development and availability of safe and effective medical products for Zika virus
- Primary areas of activity have included:

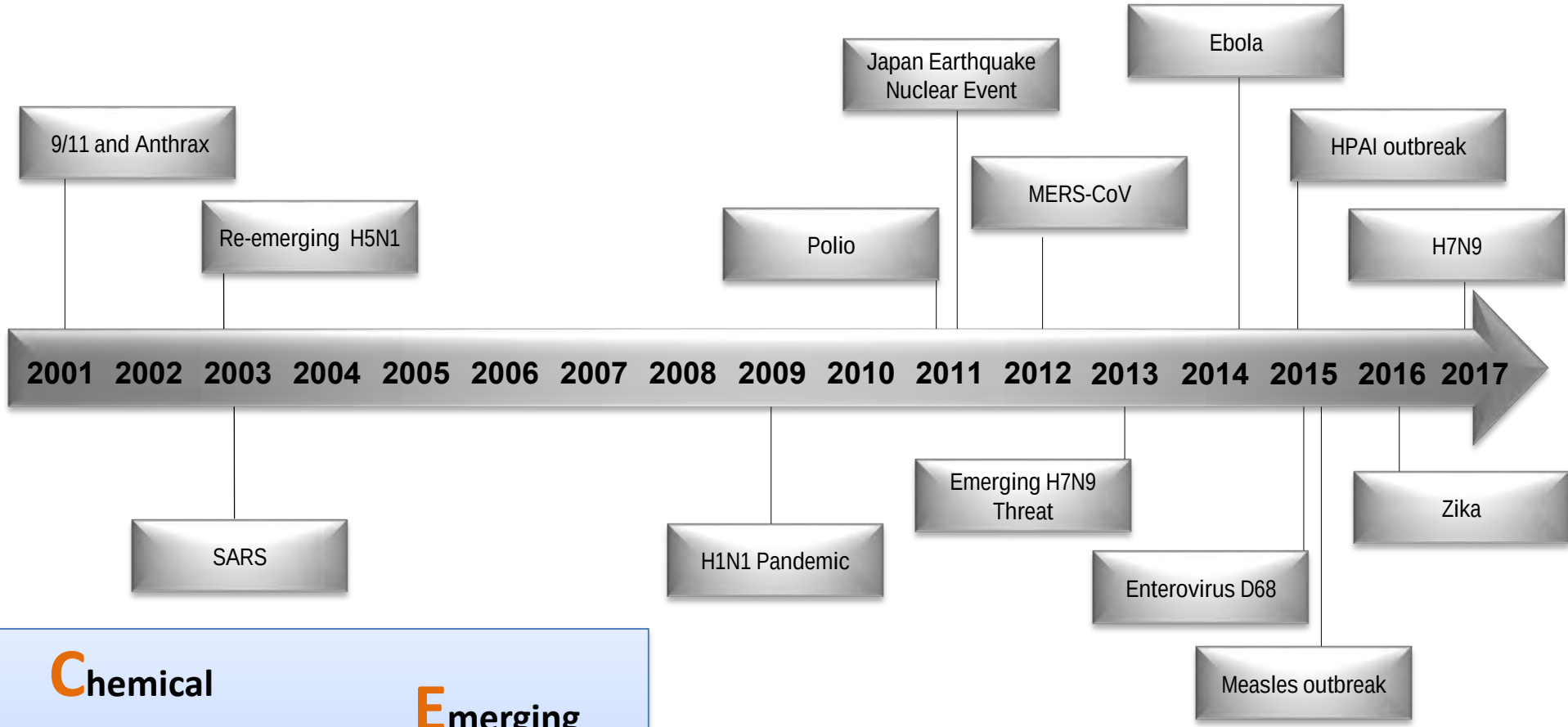
  (1) Blood safety
  (2) Clinical diagnostic tests
  (3) Vaccine and therapeutic development
  (4) Vector control
  (5) Fraudulent product monitoring

MCM Monitoring and Assessment: Beyond the Last Mile

FDA's MCM Roles

- Facilitating development of and access to safe and effective MCMs
- Legal mechanisms (e.g., EUA, IND, IDE, Expanded Access)
- Consumer protection
- Collaboration
- **Monitoring MCM use for safety and effectiveness**

Public Health Emergencies: CBRN & EID



Chemical
Biological
Radiological
Nuclear

\+

Emerging
Infectious
Diseases

Source: HHS/ASPR.

MCM Monitoring and Assessment (M&A)

The U.S. government has a limited capacity to rapidly collect and analyze public health emergency (PHE) MCM safety and effectiveness data, especially during a PHE response.

…now what?

External Partners and Stakeholders

M&A Issues

- Regulatory science & regulatory policy
- Emergency preparedness and response
- Technical, administrative, legal, and logistical challenges

How is assessment different in a public health emergency?

PHE

- Intent – respond and mitigate
- Unplanned / Unexpected
- Uncontrolled or no data collection
- Undefined number of individuals
- Simultaneous administration / multiple products
- Requires rapid decision-making
- Little or no tracking / monitoring
- Lack of / limited clinical provider oversight
- Limited reporting and information dissemination

TRADITIONAL R&D

- Intent – generalizable knowledge
- Planned / Deliberate
- Well-controlled clinical trials
- Defined number of individuals
- Stepwise progression / single product administration
- Allows more time for decision-making
- Strict oversight and monitoring
- Principal investigator / clinical study staff interaction
- Informed consent/IRB
- Clearly defined reporting requirements and information sharing

Progress to Date

FDA

EvGen Evidence Generation

openFDA

PUBLIC HEALTH EMERGENCY PHEMCE MEDICAL COUNTERMEASURES ENTERPRISE

DEPARTMENT OF VETERANS AFFAIRS · DEPARTMENT OF DEFENSE · UNITED STATES OF AMERICA

MDEpiNet

UNITED STATES CRITICAL ILLNESS AND INJURY TRIALS GROUP USCIITG

Sentinel Initiative

RAPID FDA

The National Academies of SCIENCES ENGINEERING MEDICINE

Food and Drug Administration MEDWATCH

Innovation in Medical Evidence Development and Surveillance

BD4P

MDIC MEDICAL DEVICE INNOVATION CONSORTIUM

NEST

VAERS Vaccine Adverse Event Reporting System

Image courtesy of BARDA.

Recent M&A Activities

- National Academies of Sciences, Engineering, and Medicine (NASEM) Workshop (June 6-7, 2017)
  - *Building a National Capability to Monitor and Assess Medical Countermeasure Use During a Public Health Emergency: Going Beyond the Last Mile: Proceedings of a Workshop*
  - http://nationalacademies.org/hmd/reports/2017/building-a-national-capability-to-monitor-and-assess-mcm-use-during-a-phe-proceedings.aspx
- PHEMCE MCM Monitoring and Assessment Integrated Program Team (IPT)
- Patient-Centered Outcomes Research Trust Fund (PCORTF)
- FDA's Real-Time Application for Portable Interactive Devices (RAPID) System
- FDA Sentinel Initiative

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
- **MCM Monitoring and Assessment**
  - https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm561377.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

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Website: www.fda.gov/MedicalCountermeasures

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gregory.measer@fda.hhs.gov

AskMCMi@fda.hhs.gov