



EXPEDITED DEVELOPMENT PROGRAMS AND EMERGENCY ACCESS MECHANISMS

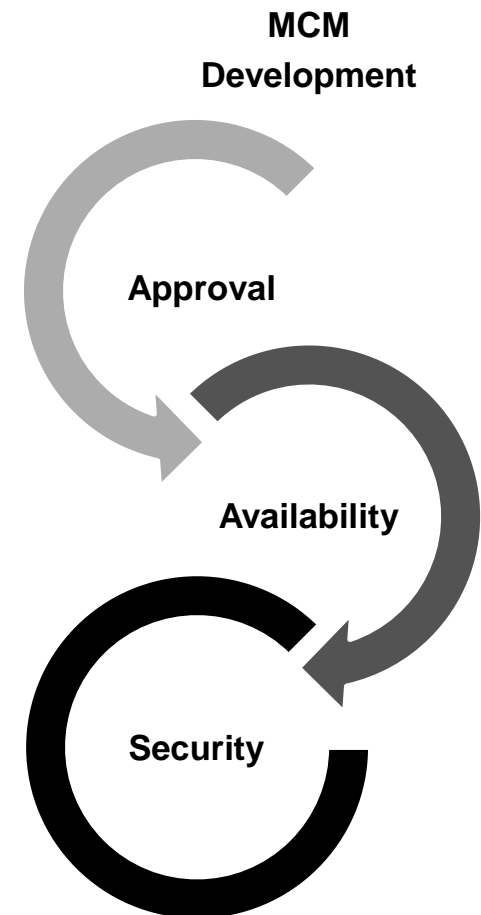
**UTMB-FDA Course: Achieving Data Quality and Integrity in Maximum
Containment Laboratories**

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Office of Counterterrorism and Emerging Threats (OCET)

- Facilitate the **development** and **availability** of safe, effective MCMs
 - Engage with product sponsors throughout product development
 - Use legal/regulatory mechanisms to facilitate emergency use
 - Monitor for adverse events and assess benefit
 - Ensure laws and policies support this goal
- Point of entry on policy, planning for global health security, counterterrorism, emerging threats
- Identify and resolve complex scientific and regulatory challenges for MCMs



Overview

- Expedited Development Programs for Serious Conditions
 - Fast Track
 - Breakthrough therapy
 - Priority review designation
 - Accelerated approval
 - MCM-Specific Review Provisions
- Emergency Access Mechanisms
 - Expanded Access
 - Emergency Use Authorization (EUA)
- Other Emergency Use Authorities



(1) Expedited Development Programs for Serious Conditions

For detailed information on these programs (excluding those specific to MCMs), see FDA's Guidance document "Expedited Programs for Serious Conditions—Drugs and Biologics," May 2014

Fast Track Designation

(FD&C Act § 506(b))

- Qualifying Criteria
 - Serious condition, and
 - Nonclinical or clinical data demonstrate the potential to address an unmet medical need, or
 - Qualified Infectious Disease Product designation
- Features
 - Frequent interactions with review team
 - Rolling review

Breakthrough Therapy Designation

(FD&C Act § 506(a))

- **Qualifying Criteria**
 - Serious condition, and
 - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on a clinically significant endpoint(s)
- **Features**
 - Intensive guidance on efficient drug development program, beginning as early as phase 1, and may include alternative clinical trial designs
 - Organizational commitment toward review
 - Rolling review



Priority Review Designation

(Prescription Drug User Fee Act of 1992, FDC&C Act §§ 524, 529)

- Qualifying Criteria
 - Serious condition, and
 - Demonstrates potential to be a significant improvement in safety or effectiveness, or
 - Qualified Infectious Disease Product designation, or
 - Submitted with a priority review voucher (i.e., neglected tropical disease, rare pediatric disease)
- Features
 - Marketing application reviewed in 6 months (compared to 10 months for standard review)

Accelerated Approval Pathway (FD&C Act § 506(c))

- 21 CFR 314, subpart H & 601, subpart E
- Qualifying Criteria
 - Serious condition, and
 - Provides meaningful advantage over available therapies, and
 - Demonstrates an effect on a surrogate endpoint or an intermediate clinical endpoint
 - Surrogate endpoint = marker that is reasonably likely to predict clinical benefit.
 - Intermediate clinical endpoint = Clinical endpoint that can be measured earlier than irreversible morbidity or mortality.

Accelerated Approval Pathway.. Continued

- Discussions about endpoints and confirmatory trials should begin with the review division early in development
- Features
 - Allows approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
 - Subject to expedited withdrawal
 - Requires confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit

MCM-Specific Review Provisions

(FD&C Act § 565)

- Ensure appropriate FDA involvement in interagency activities related to advanced R&D and any flexible manufacturing activities [§ 565(b)(1)–(2)]
- Promote FDA MCM expertise by [§ 565(b)(3)(A)–(D)]:
 - Ensuring FDA personnel reviewing countermeasures are appropriately trained and informed of material threat assessments (MTAs);
 - Holding public meetings at least 2 times/year to encourage exchange of scientific ideas;
- Maintain teams with MCM expertise (inc special populations) to [§ 565(b)(4)]:
 - Consult with MCM experts (including sponsors) to help identify and resolve issues relating to approval/licensure/clearance, through public meetings and workshops; and
 - Improve and advance regulatory science to inform approval processes and to meet the needs of special needs populations
- Consider the material threat posed by identified agent(s) when evaluating applications and include personnel with MCM training/experience on review teams. [§ 565(e)]
- Develop Regulatory Management Plans [§ 565(e)]
 - An agreement with negotiated milestones that trigger meetings based on performance targets and feedback
 - Note: typically FDA applies accelerated approval, fast track, orphan designations, and special protocol assessment provisions

(2) Emergency Access Mechanisms

- For more information about expanded access, see FDA's Expanded Access Website:
 - <http://www.fda.gov/newsevents/publichealthfocus/expandedaccesscompassionateuse/default.htm>
 - Draft guidance entitled “Expanded Access to Investigational Drugs for Treatment Use,” May 2013
- For more information about Emergency Use Authorization (EUA) and other emergency use authorities, see draft guidance, “Emergency Use Authorization of Medical Products and Related Authorities,” April 2016

Clinical Trial versus Emergency Access?

- Depends on the circumstances of the emergency, what is known about the product, operational considerations, risks and benefits
- Clinical trials under an IND/IDE may be the most ethical and fair means to make available investigational products (drugs, biologics, and devices) during an emergency
 - Limited supplies, need to assess product (most efficient way to learn if a candidate product helps or harms patients)
 - Adaptive trial designs, randomization to standard of care
 - Approval by an Investigational Review Board (IRB) and Informed Consent
- In other cases, emergency access to unapproved products outside of a trial may most appropriate.

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

Without these mechanisms, certain preparedness and response activities could otherwise violate provisions of the FD&C Act:

- Some MCMs needed for a response might not be approved, licensed, or cleared by FDA (e.g., Ebola)
- Some MCMs needed for a response might be approved by FDA, but not for the emergency use (e.g., for a new indication)
- Some might be approved for the emergency use, but:
 - Need to be dispensed (e.g., at PODs) without individual prescriptions and/or by someone who is not a licensed health care professional, and with emergency use instructions (e.g., fact sheets)
 - MCMs might be used beyond their manufacturer-labeled expiration date
- Also, to ensure the Public Readiness and Emergency Preparedness (PREP) Act protections apply

What are the legal/regulatory mechanisms for emergency use of MCMs?

- **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)
- **Emergency Use Authorization (EUA)**
 - FD&C Act § 564
 - Established by Project BioShield Act (2004)
 - Amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) (Public Law 113-5)
- **Emergency use authorities**
 - FD&C Act §§ 564A, 505-1, and 564B
 - Established by PAHPRA

Expanded Access (FD&C Act § 561)

- Allows access to investigational products for a serious or immediately life-threatening disease or condition
- Preserves IND/IDE patient safeguards:
 - Informed consent
 - Approval by an Institutional Review Board (IRB)
- Investigator/ physician determines (and FDA must confirm):
 - There is no comparable or satisfactory alternative therapy available
 - Probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition
- FDA determines:
 - Based on available information, there is sufficient evidence of safety and effectiveness to support use given the context of the disease or condition
 - That providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval

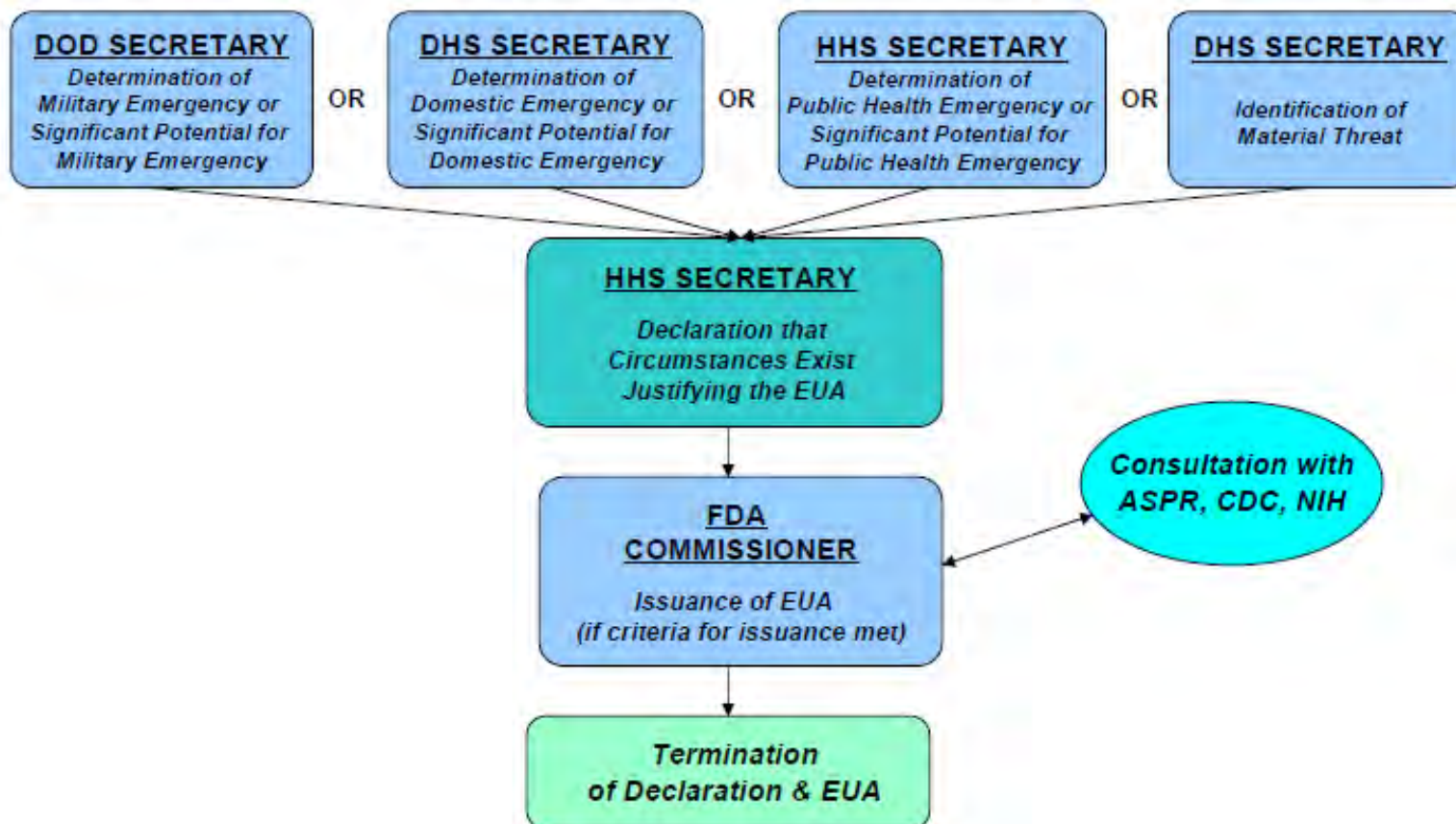
Expanded Access ... continued

- Single Patient INDs/IDEs (e-IND= emergency IND):
 - FDA granted multiple requests for Ebola therapeutics prior to initiation of clinical trials
 - Requests can come from product sponsors or physicians
- Treatment INDs/IDEs (access protocols, access INDs):
 - When there are multiple e-IND requests for the same product, the sponsor may consolidate for efficiencies and to facilitate safety signal detection
 - FDA typically requests sponsors to submit information to demonstrate clinical trials' enrollment is not being hindered by an access protocol

EUA Authority (FD&C Act § 564)

- With an EUA, FDA can authorize for use in CBRN emergencies the:
 - 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)
- 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
- Overview of requirements for EUA issuance:
 - DHS, DoD, or HHS Secretary makes a specific type of **determination** of an emergency or “significant potential” for an emergency
 - Allows for issuance EUAs for preparedness purpose (staging, stockpiling, rapid initial use)
 - HHS Secretary issues a **declaration** that circumstances exist to justify EUA issuance based on 1 of the 4 types of determinations
 - FDA ensures EUA **criteria for issuance** are met and issues the EUA when appropriate

Summary of Process for EUA Issuance (FD&C Act § 564, as amended by PAHPRA)



EUA Authority ... continued

- Criteria:
 - Serious or life-threatening illness/condition caused by chemical, biological, radiological, nuclear agent
 - Reasonable belief product may be effective
 - Known/potential benefits outweigh known/potential risks
 - No adequate, approved, available alternative to the product
- Conditions of authorization = safeguards, such as:
 - Information on emergency use (for example, fact sheets for recipients and health care professionals)
 - Including notification that the product is not FDA-approved
 - Dispensing/screening procedures
 - Record keeping and monitoring of adverse events
 - Collection of information
 - Conditions also clarify roles (e.g., CDC, laboratories)

EUAs Issued (1)

EUAs Issued by FDA			
Year	MCM	Requester	Status
Anthrax (<i>Bacillus anthracis</i>)			
2005	Anthrax Vaccine Adsorbed (AVA)	DoD	Terminated
2008 (reissued 2009, 2010, 2011)	Doxycycline hydrochloride 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*
2009 H1N1 Influenza Pandemic			
2009-2010	Antivirals (3)	HHS (CDC)	Terminated (all H1N1 EUAs)
	IVDs (18)	Various	
	Disposable N95 respirators	HHS (CDC)	
Novel Influenza A (H7N9) Virus			
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 Corporation	Current
2014	A/H7N9 Influenza Rapid Test	Arbor Vita Corporation	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.	aitona Diagnostics GmbH	Current
Enterovirus D68 (EV-D68)			
2015	CDC EV-D68 2014 rRT-PCR Assay	HHS (CDC)	Current
Zika Virus			
2016	CDC Zika MAC-ELISA (IgM)	HHS (CDC)	Current
2016	CDC Zika Triplex rRT-PCR Assay	HHS (CDC)	Current

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

EUAs Issued (2): for Ebola Virus

Ebola EUAs Issued by FDA			
Year	MCM	Requester	Status
2014 <i>(reissued in 2014)</i>	DoD EZ1 Real-time RT-PCR Assay	DoD	Current
2014 <i>(reissued in 2015)</i>	CDC Ebola VP40 rRT-PCR Assay	HHS (CDC)	Current
2014 <i>(reissued in 2015)</i>	CDC Ebola NP rRT-PCR Assay	HHS (CDC)	Current
2014 <i>(reissued in 2015)</i>	FilmArray NGDS BT-E Assay	BioFire Defense, LLC	Current
2014	FilmArray Biothreat-E test	BioFire Defense, LLC	Current
2014 <i>(reissued in 2014)</i>	RealStar Ebolavirus RT-PCR Kit 1.0	altona Diagnostics, GmbH	Current
2014	LightMix Ebola Zaire rRT-PCR Test	Roche Molecular Systems, Inc.	Current
2015 <i>(reissued in 2015)</i>	ReEBOV Antigen Rapid Test	Corgenix, Inc.	Current
2015	Xpert Ebola Assay	Cepheid	Current
2015	OraQuick Ebola Rapid Antigen Test (use with whole blood)	OraSure Technologies, Inc.	Current
2016	OraQuick Ebola Rapid Antigen Test (use with cadaveric oral fluid)	OraSure Technologies, Inc.	Current

Other Emergency Use Authorities (FD&C Act § § 564A, 564B)

- Authorities for eligible MCMs– FDA-approved/cleared for the 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) [§ 564A(d)]
 - Emergency use instructions (EUI) (CDC) [§ 564A(e)]
 - Expiration dating extensions (FDA) [§ 564A(b)]
 - Current Good Manufacturing Practices (CGMP) waivers (FDA) [§ 564A(c)]
 - Risk Evaluation and Mitigation Strategy (REMS) waivers (FDA) [§ 505-1(k)]
- 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, or licensure or EUA issuance



THANK YOU!

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