MCM Policy Updates following the 2013 Enactment of PAHPRA

Session: What's New in MCM Science and Policy at FDA

12th Annual Emerging Infectious Diseases + Biodefense

June 6, 2014

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OVERVIEW

- FDA MCM Regulatory Policy Roles
- Need for Special Legal/Regulatory Mechanisms to Facilitate the Use of MCMs during Emergencies
- PAHPRA Updates
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  (2) MCM Product Development Provisions
- Looking Forward and Additional Resources

FDA MCM Regulatory Policy Roles

Medical Countermeasures Initiative (MCMi)

- To promote the *development* of MCMs by enhancing FDA's regulatory processes and fostering establishment of clear regulatory pathways for MCMs; to facilitate *timely access* to MCMs by establishing effective regulatory policies/mechanisms

- **3-pillar approach**:
  - Pillar I: Enhancing regulatory review processes for the highest priority MCMs and related technologies
  - Pillar II: Advancing regulatory science for MCM development and evaluation
  - **Pillar III: Modernizing the legal, regulatory, and policy framework for effective public health response**
    - **Facilitate MCM development, evaluation, and availability by ensuring that laws, regulations, and policies support preparedness and response**
    - **Ensure legal preparedness**

Examples of MCM Regulatory Policy Accomplishments

- PAHPRA implementation (amendments to FDA's statutory authority to enhance MCM activities)
- EUA activities (pre-EUA activity, EUA issuance)
- Expiration dating solutions for critical MCM stockpiles
- Increased level of FDA engagement/communications with stakeholders (academia, government partners, industry/trade associations), including:
  - Development of MOUs [e.g., DARPA (2011, updated 2012), ASPR (2012), PHEMCE (2014)]
  - Outreach/webinars/educational tools
  - Support for regulatory science activities and meetings, Advisory Committee meetings, and public workshops

Need for Special Legal/Regulatory Mechanisms to Facilitate the Use of MCMs during Emergencies

What Makes MCMs Different?

- Nature of disease/condition presents unique development challenges (e.g., studies of efficacy under Animal Rule)
- Certain response activities could violate FD&C Act provisions:
  - Some MCMs needed for a response might not be FDA-approved for any use, or might be approved by FDA but not for the use needed during an emergency
  - MCMs might be dispensed (e.g., at PODs) without individual prescriptions and/or by volunteers or staff who are not licensed health care professionals
  - Emergency use instructions (e.g., fact sheets) about the MCM, but which are not part of the MCM's FDA-approved labeling, might be given to recipients of the MCM and to the health care professionals administering them
  - MCMs might be used past their manufacturer-labeled expiration date
- Special legal protections under the Public Readiness and Emergency Preparedness (PREP) Act for a range of MCM actors and MCM activities (product development through use) may be desired

Emergency Uses of MCMs: Legal/Regulatory Mechanisms

- **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
  - Amended by PAHPRA

- **Emergency use authorities**
  - FD&C Act §§ 564A, 505-1, and 564B
  - Established by PAHPRA

Expanded Access Mechanisms

- To be used in human testing in the U.S., in most cases a drug (including a biologic drug) must be covered by an IND and a device by an IDE
- INDs and IDEs are reviewed by FDA, which has the authority to halt investigations proposed to be carried out under these applications
- IND and IDE regulations require patient safeguards (e.g., in most cases, IRB supervision, informed consent by subjects, and reporting to FDA)
- In some circumstances, may be an appropriate mechanism for use of an unapproved product during a public health emergency, for example:
  - When there is little or no safety data to enable EUA risk-benefit assessment
- Types of INDs
  - Individual patients (including for emergency use) (21 CFR 312.310)
  - Intermediate-size patient populations (21 CFR 312.315)
  - Large patient populations under a treatment IND (21 CFR 312.320)

PAHPRA Updates

Pandemic and All-Hazards Preparedness Reauthorization Act of 2013

- Enacted March 13, 2013 (Public Law 113-5)
- Title III. Enhancing Medical Countermeasure Review (sections 301-307)
  - Supports goals FDA is already aggressively working to advance through MCMi
  - Recognizes FDA's vital role in supporting our nation's public health preparedness and response efforts and advancing the development and availability of MCMs for CBRN emergencies
  - Facilitates MCM product development, emergency preparedness, and rapid response capabilities:
    (1) Amends the EUA authority (FD&C Act §564)
    (2) Establishes authorities related to the emergency use of MCMs (FD&C Act §§564A and 505-1)
    (3) Includes provisions to enhance MCM development activities and expertise

Emergency Use Authorities
(as amended or established by PAHPRA)

EUA Authority: Summary

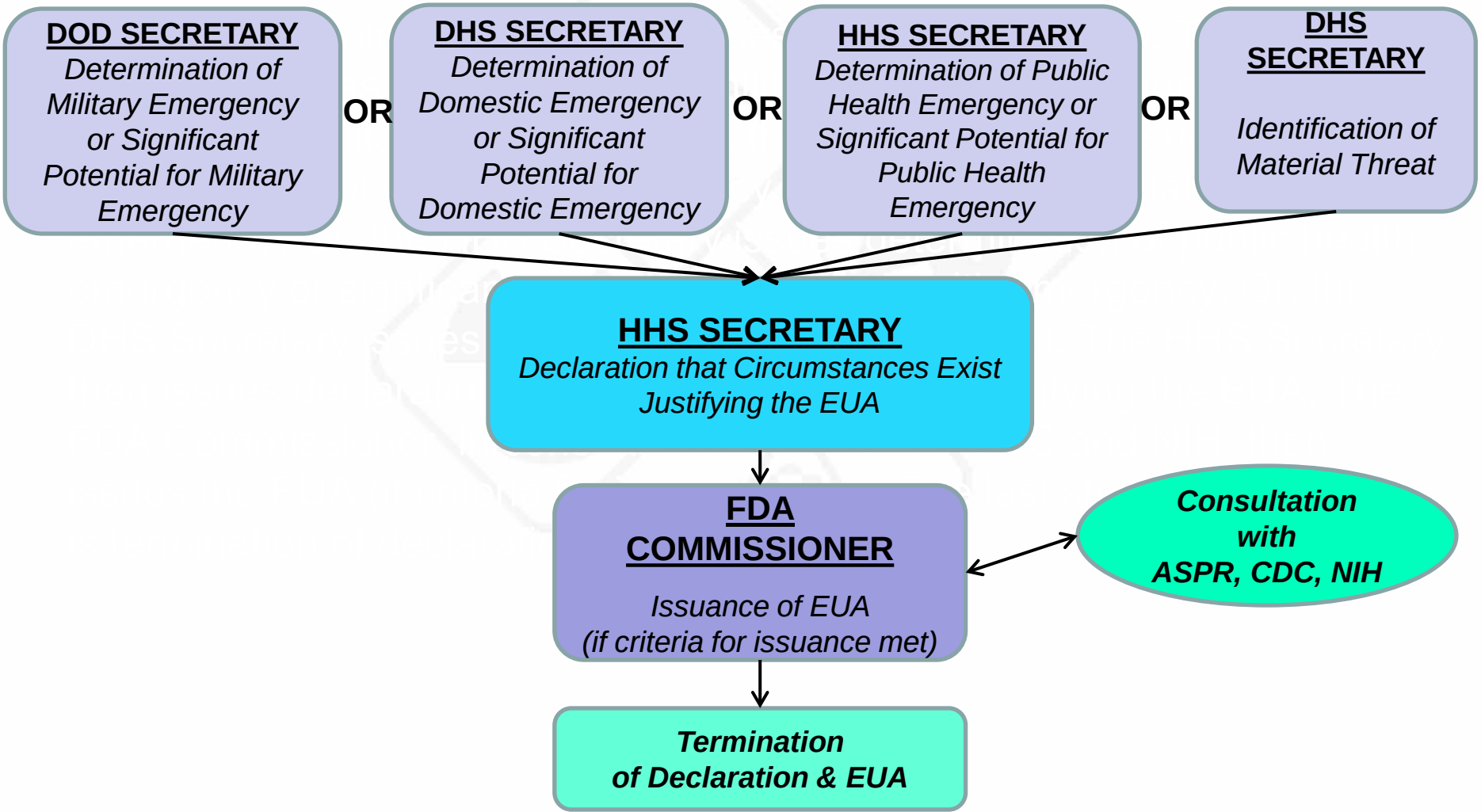
- After statutory criteria for issuance are met, FDA can authorize for use in CBRN emergencies the:
  - Use of an unapproved MCM or
  - Unapproved use of an approved MCM
- When scientific evidence is available to support MCM use in a CBRN emergency, issuing an EUA enables response stakeholders to use, or prepare to use, an MCM without violating provisions of the FD&C Act
- An EUA also helps to ensure PREP Act coverage (42 U.S.C. 247d-6d)
  - The PREP Act authorizes HHS Secretary to issue a declaration to provide liability immunity to "covered persons" for claims causally related to the development, distribution, administration, or use of "covered countermeasures" (including drugs, biologics, and devices that are approved; used under an EUA, IND, or IDE; or approved and used under PAHPRA emergency use authorities)

EUA Authority: PAHPRA Amendments

- Gives FDA clearer authority to issue EUAs before an emergency
  - Allows issuance of an EUA without declaring that an "emergency" exists (e.g., the EUA determination can be based on a "significant potential" for a public health emergency or on the identification of a material threat)
  - To allow for staging (moving product in interstate commerce), stockpiling, creating fact sheets, and rapid initial use
  - Criteria for issuance are the same whether the EUA is issued before or during an emergency
- Eliminates 1-year automatic expiration of the HHS declaration that supports EUA issuance
- Expands the time period for collection and analysis of data about an MCM's safety and clinical benefit beyond the effective period of the EUA
- Expressly permits FDA, when issuing an EUA for use of a diagnostic test, to categorize the test to allow it to be used at a point-of-care site (i.e., for purposes of CLIA waiver)

Summary of Process for EUA Issuance

(FD&C Act § 564, as amended by PAHPRA)



Example of EUA Issuance following PAHPRA

- **Quidel H7N9 IVD EUA**
  - January 2014: Quidel Corporation requested an EUA for use of the "Lyra™ Influenza A Subtype H7N9 Assay" (an uncleared IVD) for preparedness
  - April 19, 2013: HHS Secretary determined "*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 United States citizens living abroad and that involves the avian influenza A (H7N9) virus*" (78 FR 25273)
  - April 19, 2013: HHS Secretary declared "*that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection of the avian influenza A (H7N9) virus*" (78 FR 25273)
  - February 14, 2014: FDA issued an EUA for the Quidel H7N9 IVD
  - Additional H7N9 EUA information is available at: **http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm**

Summary of EUA Activities

Year	MCM	Requester	Status
	Anthrax [*Bacillus anthracis*]		
2005	Anthrax Vaccine Adsorbed (AVA)	DoD	Terminated
2008	Doxycycline hyclate tablets (in USPS home & workplace kits)	HHS (ASPR/ BARDA)	Amended in 2009, 2010, 2011 (see row below)
2011	Doxycycline hyclate 100 mg oral tablets (in National Postal Model home & workplace kits)	HHS (ASPR/ BARDA)	Current
2011	All oral formulations of doxycycline (mass dispensing)	HHS (CDC)	Current*
	2009 H1N1 Influenza Pandemic		
2009-2010	Antivirals (3)	HHS (CDC)	Terminated
2009-2010	IVDs (18)	Various	Terminated
2009-2010	Disposable N95 Respirators	HHS (CDC)	Terminated

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

Summary of EUA Activities (cont.)

Year	MCM	Requester	Status
	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	CDC Novel Coronavirus 2012 Real-time RT-PCR Assay	HHS (CDC)	Current

Preparedness Activities

- Pre-EUA activity
  - FDA works with product sponsors and government agencies to facilitate the development of pre-EUA packages that can form the basis of an EUA request and issuance when circumstances justify
  - Pre-EUA packages contain data and information about the safety and efficacy of the product, its intended use under an EUA, and information about the potential emergency situation that might unfold to allow FDA to begin review and assist in development of the conditions of the authorization as well as necessary accompanying information
- Pre-positioning of MCMs under new §564B of the FD&C Act
  - To facilitate rapid deployment during an actual emergency, PAPHRA allows pre-positioning of MCMs by or on behalf of government entities (federal, state, local) in anticipation of FDA approval, clearance, or licensure, or EUA issuance

New Emergency Use Authorities

- For FDA-approved MCMs intended for use during CBRN emergencies, certain activities now are allowed *without FDA issuing an EUA* and without rendering a product unapproved, adulterated, or misbranded
- PAHPRA establishes emergency use authorities for certain approved MCMs to facilitate public health and health care preparedness/response:
  - Emergency dispensing orders [§564A(d)]
  - Expiration dating extensions [§564A(b)]
  - Emergency use instructions [§564A(e)] (*delegated to CDC in Dec. 2013*)
  - CGMP waivers [§564A(c)]
  - REMS waivers [§505-1]
- These authorities preserve otherwise applicable liability protections (e.g., PREP Act) for responders and others involved in MCM planning, preparedness, and response

PAHPRA MCM Development Provisions

PAHPRA and MCM Development

- PAHPRA codifies and builds on FDA efforts that were already being implemented under the MCMi to provide the highest quality and most timely guidance possible to stakeholders engaged in MCM development

- For example, PAHPRA:
  - Expands current Special Protocol Assessment requirements to pivotal animal studies supporting claims of efficacy [§505(b)(5)(B)]
  - Establishes a procedure for FDA to meet with MCM sponsors developing animal models [§565(d)] (see our website)
  - Promotes MCM expertise at FDA (e.g., reviewer training on MCM issues, 2 public meetings/year to encourage exchange of scientific ideas, etc.) [§§565]
  - Ensures appropriate FDA involvement in interagency MCM advanced research and development activities [§§505(b)(3)]

PAHPRA and MCM Development (cont.)

- Requires FDA to maintain teams with MCM expertise to identify and resolve scientific issues that may present obstacles to MCM development and approval (i.e., FDA's current MCMi Action Team approach) [§505(b)(4)]
- Requires FDA to finalize guidance on development of animal models for purposes of establishing claims of efficacy [§505(c)]
- Ensures pediatric experts are consulted, and the needs of pediatric populations are appropriately considered, in developing MCMs [§307 of PAHPRA]
- Regulatory Management Plans [§565]
  - Requires establishment of formal processes for FDA−sponsor interactions regarding development and review of eligible, high priority MCMs
  - FDA is working with BARDA on establishing a process for prioritization

Looking Forward

- FDA is currently working with federal partners on interpretation and implementation of PAHPRA's MCM provisions

- FDA intends to issue guidance and other informational materials as needed, and will work with its federal partners and other key stakeholders to optimize and communicate the impact of PAHPRA on MCM-related activities. For example:
  - FDA PAHPRA Q&A for public health stakeholders (posted January 2014)
  - FDA guidance on MCM emergency use authorities (in progress)

- Please feel free to contact FDA at any time with questions about PAHPRA's changes and about implementation

Additional Resources

- **FDA Medical Countermeasures Initiative (MCMi)** (*including 2013 MCMi Annual Report*)
  - http://www.fda.gov/medicalcountermeasures
- **PAHPRA (Public Law 113-5)**
  - http://www.gpo.gov/fdsys/pkg/PLAW-113publ5/pdf/PLAW-113publ5.pdf
- **FDA EUA Website** (*official updates, current & terminated EUAs, questions & answers, guidance, etc*.)
  - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm
- **FDA PAHPRA Website** (*PAHPRA summary, 2014 question and answer document, official updates*)
  - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm359581.htm
- **PREP Act (HHS)**
  - http://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx

Thank you!

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