FDA'S ROLE IN MEDICAL COUNTERMEASURES: Current Issues and Challenges

WORKSHOP:

Introduction to Medical Countermeasures: Policy, Products, and Practice

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Brooke Courtney, JD, MPH
Office of Counterterrorism and Emerging Threats
Office of the Commissioner
U.S. Food and Drug Administration

Overview

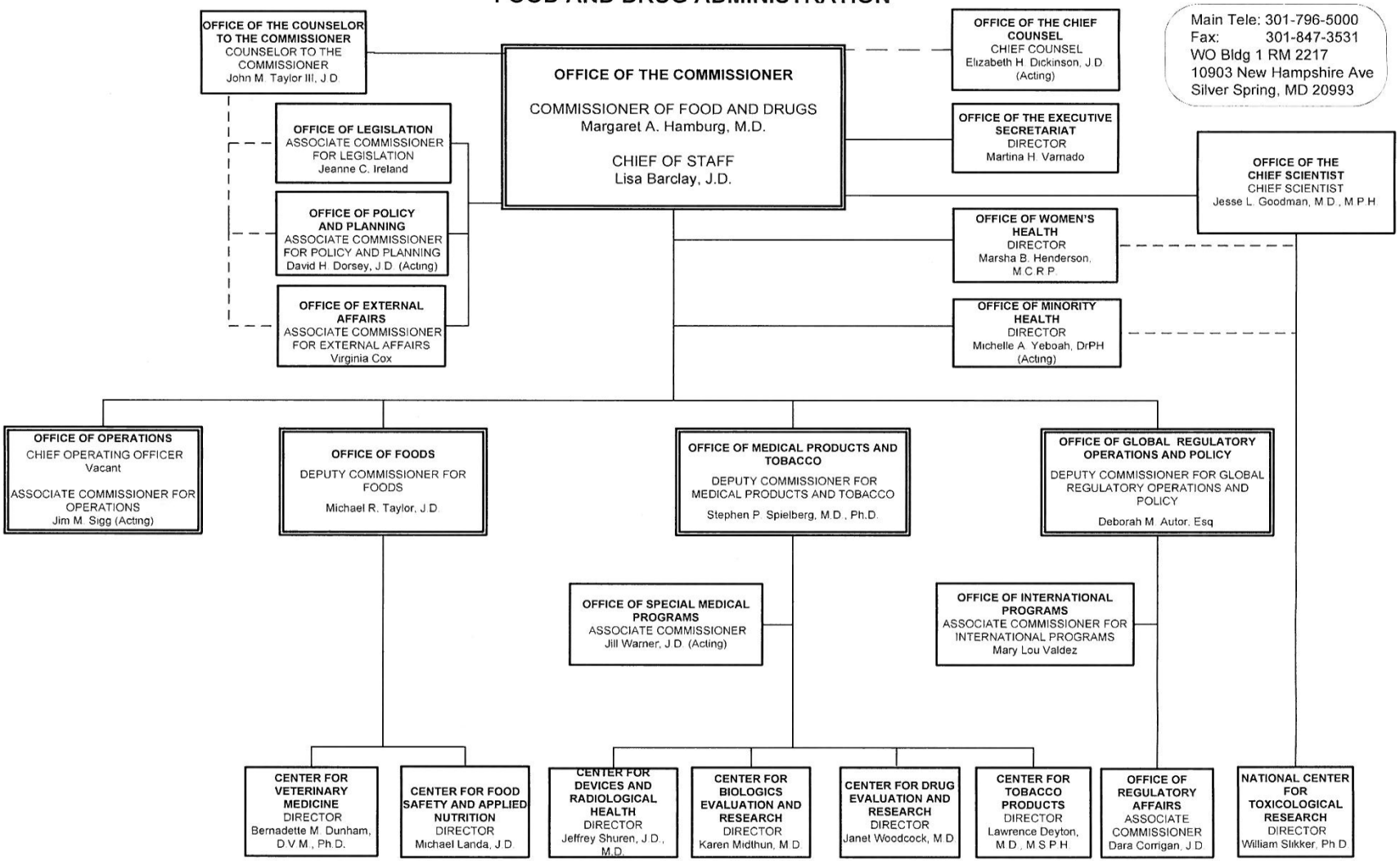
- FDA's Roles in Regulating Medical Products
- FDA's MCM Roles
- Legal and Regulatory Mechanisms for MCMs
  - Investigational New Drug Applications (INDs)
  - Emergency Use Authorizations (EUAs)
- EUA Activity
  - Doxycycline Mass Dispensing EUA
  - USPS/National Postal Model EUA
- Other Issues and Developments Related to Mass Dispensing Efforts

FDA's Roles in Regulating Medical Products

Overview of FDA's Roles

- An agency within HHS, FDA is responsible for:
  - Protecting public health by assuring foods are safe, wholesome, sanitary, and properly labeled, and human and veterinary drugs, vaccines, other biological products, and medical devices intended for human use are safe and effective
  - Protecting public from electronic product radiation
  - Assuring cosmetics and dietary supplements are safe/properly labeled
  - Regulating tobacco products
  - Advancing public health by helping to speed product innovations
  - Helping public get accurate science-based information they need to use medicines, devices, and foods to improve their health
- Geographic scope
  - 50 United States, District of Columbia, Puerto Rico, Guam, Virgin Islands, American Samoa, and other U.S. territories and possessions

FOOD AND DRUG ADMINISTRATION



Approved by the FDA Reorganization Coordinator and Principal Delegation Control Officer

FDA Regulation of Medical Products

- Among the products FDA regulates are 3 categories of diagnostic, preventive, or therapeutic products:
  - Drugs (e.g., antimicrobials)
  - Biologics (e.g., vaccines)
  - Medical devices (e.g., diagnostics, ventilators)

- Review and approval/PMA and clearance (NDA, ANDA, BLA, 510(k))
  - Sponsor submits data to seek permission to market its product with specific labeling for a specific purpose
  - No medical product is safe and effective in the abstract; it is only safe and effective for specific uses
    - Those uses are described specifically in the product's approved labeling

Risk-Benefit Analysis

- All medical products present risks
- In some cases, those risks involve significant toxicity
- Risk-benefit analysis can change depending on the conditions in which the product will be used
  - e.g.) a drug used under the supervision of a physician may present less risk than one used without such supervision

Labeling

- Ultimately, the decisions made in the FDA review are captured in the approved labeling
  - A product used inconsistent with its labeling may not have data to show that it is either safe or effective for that use
  - The risk-benefit analysis may change if the conditions of use change
- All communications by marketers to health care professionals and patients concerning the product must be consistent with the approved labeling

Expiration Dating

- Pharmaceutical labeling generally includes an expiration date

- Determined on basis of FDA review of stability studies performed by the sponsor (these studies show that a drug does not degrade to the point that it no longer meets its specifications over a period of 2 years, for example)

- In some cases, testing may show that the drug would still be within its specifications for a longer period (e.g., Shelf-Life Extension Program)

Current Good Manufacturing Practices (CGMPs)

- Methods by which manufacturers, holders, and transporters of drugs, biologics, or devices assure that every product they make, hold, or transport is—and continues to be until it is used—safe and effective

- Failure to comply with CGMPs (and for devices, failure to comply with the quality system regulations) makes a product “adulterated” and its distribution or sale illegal

Enforcement Discretion

- FDA enforces the Federal Food, Drug, and Cosmetic (FD&C) Act and certain related statutes (e.g., provisions of the Public Health Service Act relating to approval of biologic products)

- FDA also enforces its regulations, which are based on those statutes

- In some cases, as with all law enforcement agencies, FDA recognizes that there are technical violations of its statutes and regulations for which enforcement is inappropriate

Practice of Medicine

- FDA generally does not regulate the practice of medicine
  - Once a product is approved or cleared, a health care professional has the freedom to use that product for any purpose, even inconsistent with its labeling
- But, FDA and the courts are very strict in preventing marketers from promoting products for uses for which they are not approved or cleared

How Does This All Apply to MCMs?

- Some countermeasures are intended to be used consistent with their approved labeling
  - No need for further review/authorization
- Other countermeasures are intended to be used in ways beyond their approved labeling, such as:
  - without a prescription
  - in different dosing regimens or for different age groups
  - with different information for recipients of the MCM
- Other countermeasures are not yet approved for any use, but might be helpful for a response because of the lack of other suitable alternatives

FDA's MCM Roles

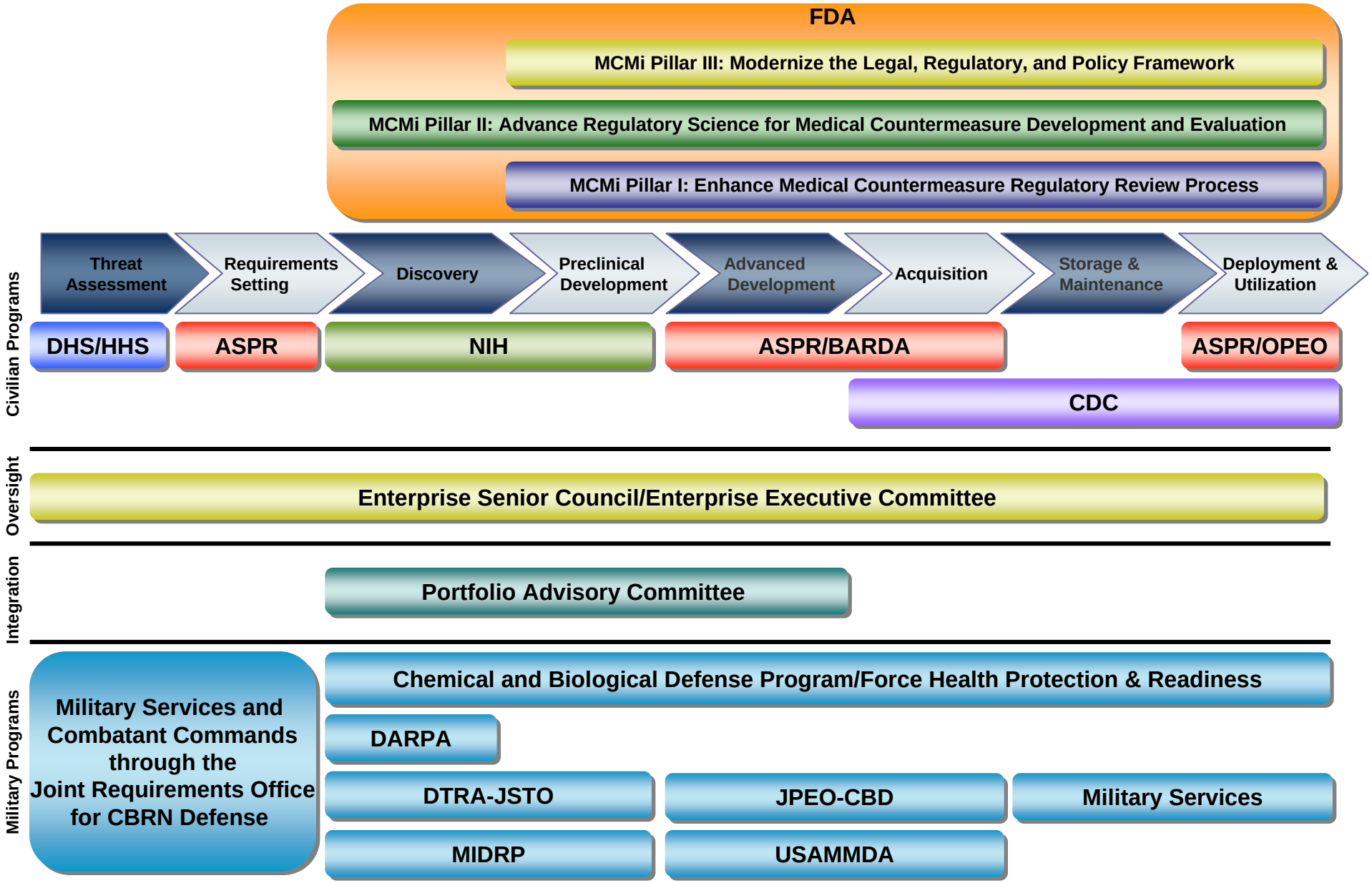
FDA's MCM Functions

- Overarching functions
  - Review and approval
  - Enforcement
  - Communication
- Centers (CDER, CBER, CDRH)
  - Product-specific scientific and technical expertise
  - Objective regulatory review
  - Early engagement with product developers
- Office of Crisis Management (OCM)

Office of Counterterrorism and Emerging Threats (OCET)

- Coordinates portfolio of FDA counterterrorism and pandemic influenza policy and planning initiatives
- Develops and coordinates implementation of FDA policies to ensure safe and effective medical products are available to counter chemical, biological, radiological, and nuclear (CBRN) agents
- Collaborates closely with FDA Centers/Offices and external partners to develop and coordinate implementation of preparedness plans and programs to counter emerging threats
- Coordinates FDA's Medical Countermeasures Initiative (MCMi)
- Leads FDA's Emergency Use Authorization (EUA) activities

Enterprise Partner Roles



FDA's Legal and Regulatory Mechanisms for MCMs

INDs

- 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
  - A device must be covered by an investigational device exemption (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, including in most cases:
  - Institutional Review Board (IRB) supervision
  - Informed consent by subjects
  - Reporting to FDA

INDs

- In some circumstances, the IND authority may be an appropriate mechanism for use of an unapproved product during an emergency
- Types of INDs:
  - Emergency use IND
    - Individual/single patient access for serious diseases
  - Expanded access trial under an IND
    - Intermediate-sized patient populations
  - Treatment use IND
    - Widespread access
- Anthrax vaccine example

EUAs

- Section 564 of the FD&C Act
- In some circumstances, FDA's EUA authority may be an appropriate mechanism to authorize the use of an unapproved product, or the unapproved use of an approved product, during an emergency
- Because EUA use is not investigational, IRB approval and informed consent are not required, and alternative dispensing mechanisms can be authorized
- Published in *Federal Register* and posted on FDA website after issuance

Why Would an EUA Be Needed?

- Novel/investigational products may be the best available to meet the emergency needs
- Requirements for clinical investigations or expanded access would be difficult to meet in emergency mass dispensing or mass vaccination scenario
- Changes from approved labeling, expiration dating, dosing schedule, and prescribing requirements would render the product misbranded or unapproved
- Potential gap for PREP Act liability coverage
  - PREP Act declarations can cover MCMs for which EUAs have been issued during an emergency

EUAs

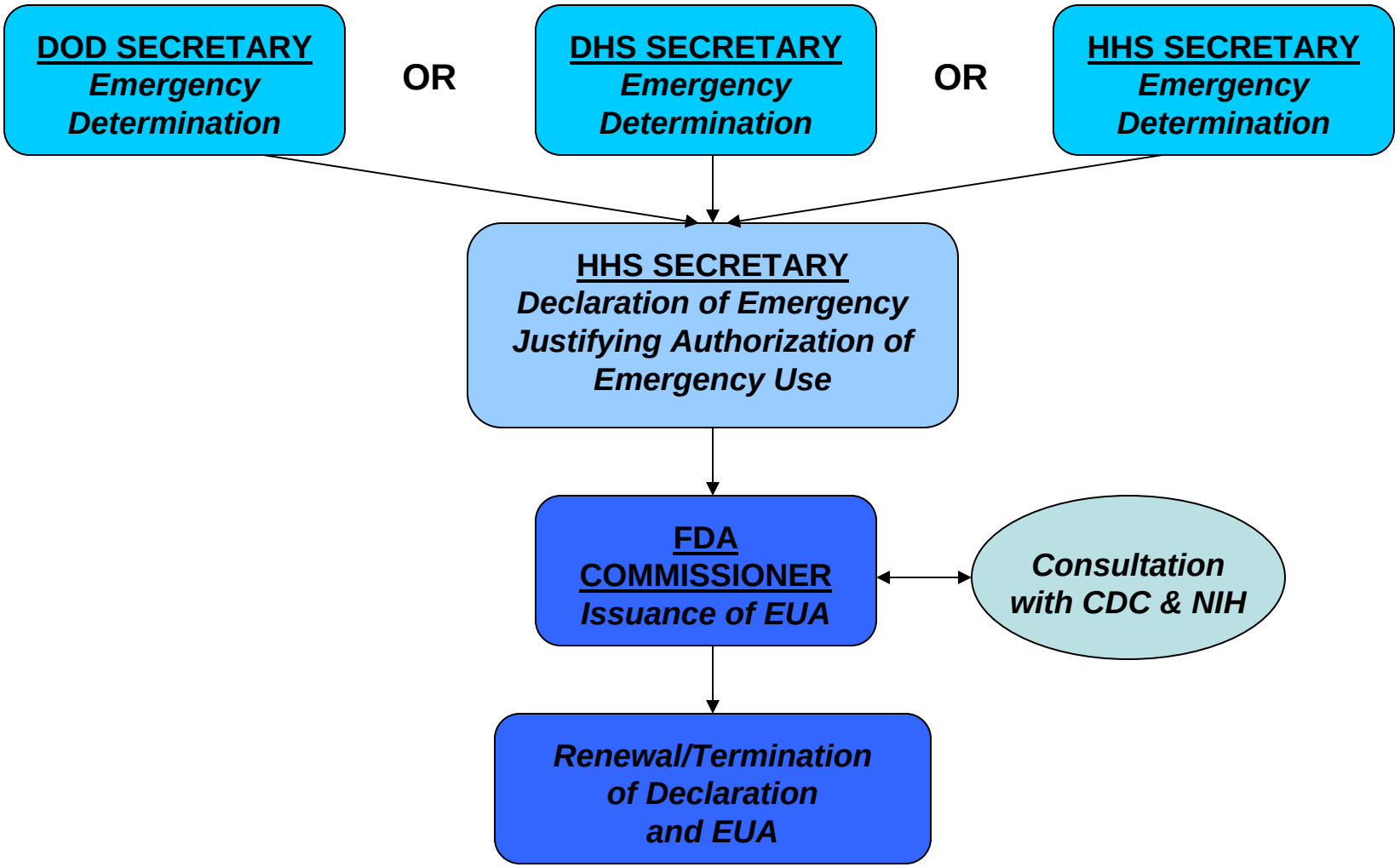
- If FDA grants an EUA request, it is finding that, in a particular type of emergency, if the EUA's conditions are observed:
  - An approved product may be used in a way inconsistent with the limitations of the approval, or
  - A product that is not yet approved may be permitted to be used (despite lacking the quantum of data that would be necessary for a full approval by FDA)

- Criteria
  - Serious or life-threatening illness/condition caused by CBRN agent
  - Reasonable belief product may be effective
  - Known/potential benefits outweigh known/potential risks
  - No adequate, approved, available alternative to the product

EUAs

- Conditions of authorization address elements of the authorization, such as:
  - Information on emergency use
    - e.g.) fact sheets for recipients and health care professionals, home preparation instructions
  - Dispensing/screening procedures
  - Record keeping and monitoring of adverse events
  - Waiver of CGMP requirements
- Conditions also clarify roles
  - e.g.) for CDC, for state and local public health agencies

Steps for Issuing an EUA



EUA Activity

Summary of EUA Activity

- DoD (anthrax vaccine) (2005) (*terminated*)
- H1N1 Influenza Pandemic (2009) (*terminated*)
    - Drugs (antivirals) (multiple EUAs)
    - Devices (IVDs) (multiple EUAs)
    - PPE
- Mass Dispensing (doxycycline) (2011) (*current*)
- National Postal Model (doxycycline home and workplace kits) (2011) (*current*)
- Pre-EUA Activity (*ongoing*)

Doxycycline Mass Dispensing EUA

- CDC submitted an EUA request to FDA for oral formulations of doxycycline products for inhalational anthrax to facilitate stakeholders' preparedness and response activities (2011)
- This EUA was possible because of:
  - DHS Secretary's determination of significant potential for a domestic emergency involving *B. anthracis* (2008)
  - HHS Secretary's declaration of emergency justifying the authorization of emergency use of doxycycline hyclate tablets for post-exposure prophylaxis (PEP) (2008, 2009, 2010)
  - HHS Secretary's renewal and amendment of the above HHS declaration to apply to all oral formulations of doxycycline (July 20, 2011)

Doxycycline Mass Dispensing EUA

- Issued on July 21, 2011
- Covers oral formulations of doxycycline (capsule, tablet, and liquid formulations) for PEP of inhalational anthrax
- Facilitates federal, state, and local preparedness and response activities, which may otherwise violate FD&C Act provisions, such as:
  - Dispensing without a prescription
  - “Minimum elements” of information to provide flexibility in developing health care professional and recipient fact sheets
  - Pre-event storage or distribution of doxycycline packaged or repackaged for emergency distribution
  - Dispensing of partial supply (e.g., 10 days) of 60-day regimen

Doxycycline Mass Dispensing EUA

- For additional details:
  - Letter of authorization
    - 76 Fed. Reg. 47197
    - http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/UCM264104.pdf
  - HHS declaration justifying the authorization of emergency use
    - 76 Fed. Reg. 44926
    - http://www.gpo.gov/fdsys/pkg/FR-2011-07-27/pdf/2011-18937.pdf
  - Doxy mass dispensing EUA questions and answers
    - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm269226.htm

National Postal Model EUA

- In 2008, FDA issued the first EUA for doxycycline hyclate tablets contained in individual workplace and household emergency antibiotic kits (HAKs) for eligible USPS employee volunteers in the Cities Readiness Initiative (CRI) and their household members
  - The EUA was amended and reissued in 2009 and in 2010
- In 2011, ASPR/BARDA submitted a request to FDA to amend the existing CRI/Postal Model EUA to reflect programmatic changes, including:
  - Updating fact sheets and screening materials
  - Removing references to PPE
  - Changing program name (“NPM”)

National Postal Model EUA

- The 2011 EUA was possible because of:
  - DHS Secretary's determination of significant potential for a domestic emergency involving *B. anthracis* (2008)
  - HHS Secretary's renewal and amendment of HHS declaration of emergency justifying the authorization of emergency use of doxycycline hyclate tablets for PEP (2008, 2009, 2010) to apply to all oral formulations of doxycycline (July 20, 2011)
- Issued on October 14, 2011
  - Covers doxycycline hyclate tablet emergency kits ("HAKs") for PEP of inhalational anthrax
  - Based on the request, limited to HAKs for eligible USPS employee volunteers in the NPM and their household members

National Postal Model EUA

- Facilitates NPM preparedness and response activities, which may otherwise violate provisions of the FD&C Act. For example, authorizes:
  - Distribution and use of emergency use information sheets (e.g., fact sheets for recipients)
  - Dispensing without all required prescription label information
  - Dispensing of partial supply of full 60-day dosage regimen
  - Pre-event storage or distribution
- For additional information, refer to Letter of Authorization:
  - 76 Fed. Reg. 72935
  - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

Other Issues and Developments Related to Mass Dispensing Efforts

Other Issues and Developments

- Shelf-Life Extension Program (SLEP)
- Relabeling
  - www.fda.gov/edrls
- Executive Order 13527
- Ciprofloxacin
- Reauthorization of Pandemic and All-Hazards Preparedness Act (PAHPA)
  - S. 1855
  - H.R. 2405

Additional Resources

- FDA State & Local Stakeholder Site
  - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm234336.htm
- EUA Questions & Answers
  - http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm153297.htm
- EUA Guidance
  - http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm
- Current & Expired/Terminated EUAs
  - http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm
- FDA Medical Countermeasures Initiative (MCMi)
  - www.fda.gov/medicalcountermeasures

Additional Resources

- Food and Drug Law Institute. Food and Drug Law and Regulation (2d ed.), *Medical Countermeasures: Emergency Preparedness and Response Roles and Authorities* (Courtney B, Sadove E). 2012. (http://www.fdli.org/pubs/books/#fdlr)
- Institute of Medicine. *Prepositioning Antibiotics for Anthrax.* 2011. (http://www.iom.edu/Reports/2011/Prepositioning-Antibiotics-for-Anthrax.aspx)
- Institute of Medicine. *Medical Countermeasures Dispensing: Emergency Use Authorization and the Postal Model: Workshop Summary.* 2010. (http://www.nap.edu/catalog/12952.html)
- Sherman SE, Foster J, Vaid S. Emergency use authority and 2009 H1N1 influenza. *Biosecur Bioterror* 2009;7(3):245-250.
- Quinn SC, et al. Public willingness to take a vaccine or drug under emergency use authorization during the 2009 H1N1 pandemic. *Biosecur Bioterror* 2009;7(3):275-290.
- Birnkrant D, Cox E. The emergency use authorization of peramivir for treatment of 2009 H1N1 influenza. *NEJM* 2009; 361(23):2204-2207.

Thank you!

Contact Information

Brooke Courtney, JD, MPH
Office of Counterterrorism and Emerging Threats
Office of the Commissioner
Food and Drug Administration
301.796.8510 (main office) / 301.796.0376 (direct line)
brooke.courtney@fda.hhs.gov

EUA.OCET@fda.hhs.gov

www.fda.gov/medicalcountermeasures