Overview

- Regulatory Framework for the Emergency Use of Medical Countermeasures (MCMs)
  - Investigational New Drug (IND)
  - Emergency Use Authorization (EUA)
  - Other Emergency Use Authorities [e.g., Emergency Use Instructions (EUI)]
CDC’s Overarching MCMs Responsibility

- Clinical
- Logistical/Operational
- Regulatory
Need for Regulatory Mechanisms

- Medical products, including SNS assets, are subject to FDA regulations.
- FDA is responsible for protecting the health of the public by assuring the quality, safety and efficacy of drugs, biologics and medical devices.
- SNS assets include:
  - FDA-approved MCMs being used for approved indications
  - FDA-approved MCMs being used for unapproved indications
  - Unapproved (investigational) MCMs
- Ensure the Public Readiness and Emergency Preparedness (PREP) Act liability protection apply.
Public Readiness and Emergency Preparedness (PREP) Act

- Provides immunity from liability (except for willful misconduct)
  - For PREP Act coverage, a product must be:
    - Approved, licensed or cleared by FDA;
    - Used under an IND or IDE; or
    - Under emergency use authorities (e.g., EUA, EUI, emergency dispensing orders)

- Authorizes a compensation fund
  - For serious physical injuries or death directly caused by use of covered countermeasures, covers medical benefits, lost wages, death benefits
Regulatory Mechanisms

- FDA-approved Status
- Investigational New Drug (IND)
- Emergency Use Authorization (EUA)
- CDC’s Emergency Use Instructions (EUI) and other FDA MCM emergency use authorities
MCMs Regulatory Mechanism: CDC’s Role/Responsibility

- Reviews available existing supportive data for the intended use of MCMs to develop, prepare, submit and update IND/Pre-EUA/EUA to FDA

- Works closely with FDA to ensure that appropriate regulatory mechanisms are in place to allow for timely deployment and optimal utilization of MCMs that are essential to preparedness and response

- IND/Pre-EUA/EUA is a dynamic process
  - Protocol/fact sheet revisions based on additional scientific data, evolving policy considerations and/or response strategies
What is an Investigational New Drug Application (IND)?

- Regulatory submission to obtain FDA’s permission to introduce an investigational drug/biologic in humans where there is **limited** or **no** human safety and efficacy data
  - Product development & clinical trials
  - Expanded access (“compassionate use”) – use outside of clinical trials for a serious disease/condition where there is no satisfactory alternative

- Informed Consent, IRB-approval & data collection/reporting (safety and efficacy)

- Isolated, individual cases to local/regional outbreak scenarios

- Limited MCM risk/benefit and supportive data

- Not conducive to large-scale events with narrow time window for MCM dispensing/administration for optimal effect
Examples of CDC Expanded Access INDs

- **Tecovirimat (ST-246, Tpoxx)**
  - Treatment of orthopoxvirus infections including smallpox vaccine complications
  - Food-effect on absorption and bioavailability
  - PK data to target human therapeutic dosing in infected-individuals
Examples of CDC Expanded Access INDs, cont.

- Anthrax vaccine in children required to be under an IND by FDA due to lack of any pediatric data
  - Informed consent process & documentation, patient-level vaccine administration information, AE monitoring and reporting, any available outcomes data
  - Implications and consideration for pre-event plans for implementing/executing IND during an emergency
Examples of Prior CDC Expanded Access INDs

- **Heptavalent Botulism Antitoxin (BAT®)**
  - Clinical use data in 249 suspected and confirmed botulism patients during 2010–2013 (prior to FDA approval in March 2013)
  - Provided first human safety and outcomes BAT data in diseased patients

- **Anthrax Immune Globulin (Anthrasil®)**
  - Clinical use data in 19 confirmed anthrax patients prior to FDA approval in March 2015

- “Investigational” MCMs stockpiled into SNS during the development pathway
  - FDA-approved MCMs under the Animal Efficacy Rule leaves gaps given the lack of human safety, efficacy, & PK data from patients with the disease
  - Post-marketing studies
What is an Emergency Use Authorization (EUA)?

- Project BioShield Act 2004, authority given to FDA Commissioner to permit emergency use in CBRN emergencies of:
  - Unapproved MCMs or
  - Unapproved use of approved MCMs

- FDA’s EUA issuance predicated on:
  - Determination of
    - Actual or potential emergency by Secretary of DHS, DoD, or DHHS or material threat by DHS secretary
  - Declaration by HHS Secretary that circumstances exist to justify EUA issuance

- FDA issues EUA if certain criteria are met
  - Serious, life-threatening disease; clinical benefit; risk/benefit; lack of adequate, FDA-approved alternatives
**Historical EUA Experiences from 2009 H1N1 Influenza Public Health Response**

<table>
<thead>
<tr>
<th>Medical Countermeasure</th>
<th>Authorized Use under EUA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamiflu</td>
<td>Use of Oseltamivir (Tamiflu) for the Treatment and Prophylaxis of Novel Influenza A (H1N1) Virus Infection; expanded age; for uncomplicated acute illness &gt; 2 days of symptoms; complicated, hospitalized patients; expiry extension; dispensing without Rx-labeling requirements; cGMP waiver</td>
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<td>Relenza</td>
<td>Use of Zanamivir (Relenza) for Prevention and Treatment of Novel Influenza A (H1N1) Virus Infection; same as Tamiflu EUA</td>
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<tr>
<td>Peramivir IV</td>
<td>Use of Intravenous Peramivir for Treatment of 2009 Pandemic Influenza A (H1N1) Virus Infection</td>
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<tr>
<td>N95 Respirators</td>
<td>Use of Non-FDA cleared, NIOSH-certified N95 Respirators and Unapproved use of Surgical N95 Respirators in Public Health Medical Emergencies</td>
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<tr>
<td>Swine Influenza Virus Real-Time RT-PCR</td>
<td>Use of the Swine Influenza Virus Real-Time RT-PCR Detection Panel to Detect Novel Influenza (H1N1); Amendments: testing of additional specimens and RT-PCR equipment</td>
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<tr>
<td>CDC Human Influenza Virus Real-Time RT-PCR</td>
<td>Implementation of the CDC Human Influenza Real-Time RT-PCR Detection and Characterization Panel for Respiratory Specimens (NPS, NS, TS, NPS/TS, NA) and Viral Culture</td>
</tr>
</tbody>
</table>

*Terminated on June 23, 2010
2009 H1N1 Pandemic EUA Experiences

- FDA-approved label – narrowly scoped
- Emergency-driven aspects of MCM distribution and usage considered unapproved uses:
  - Mass-dispensing at PODs
  - Without prescribing and dispensing label requirements
  - Partial dispensing of full labeled duration of therapy (e.g., initial start-up doses)
  - Dispensing without FDA-required medication guides (if applicable)
  - Shelf-life extension
  - Information sheets specific to the emergency

- EUA is a burdensome process for regulatory coverage regarding slight deviations from approved labeling
Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)

- Included key provisions to enhance medical countermeasures development, deployment and emergency use of medical countermeasures (MCMs)
  - Amend the Emergency Use Authorization (EUA) authority established by Project BioShield (FD&C Act § 564)
  - Establish New Emergency Use Authorities (FD&C Act § 564A and 505-1)
### PAHPRA Amendments: Emergency Use Authorities

<table>
<thead>
<tr>
<th>Unapproved MCMs or Unapproved Use of Approved MCMs</th>
<th>FDA-approved MCMs Concerning FDA-approved indication</th>
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<tbody>
<tr>
<td><strong>Amended Emergency Use Authorization (EUA)</strong></td>
<td><strong>Created New Emergency Use Authorities</strong></td>
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<tr>
<td>• Amended language on emergency determination</td>
<td>• Mass dispensing</td>
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<tr>
<td>• Eliminated 1-yr automatic termination</td>
<td>• Shelf-life extension</td>
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<tr>
<td>• Expanded time period for data collection and analysis beyond effective period of EUA</td>
<td>• cGMP waiver</td>
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<td>• REMS waiver</td>
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<td></td>
<td>• Emergency Use Instructions (EUI)</td>
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Allows for pre-positioning of MCMs (approved or unapproved) by government entities
PAHPRA: Emergency Use Instructions Authority

- **Emergency Use Instructions (EUI)**
  - Permits a designated HHS official to create and issue, and others to disseminate, emergency use instructions concerning FDA-approved conditions of use

- **Mass Dispensing** - allows mass dispensing of approved MCMs during an actual CBRNE event, without an individual prescription if permitted under State law or in accordance with an order issued by the Secretary

- **Shelf-Life Extension** - expressly authorizes FDA to extend the labeled expiration dating; products with extended expiry will not be deemed unapproved, adulterated, or misbranded

- **cGMP Waiver** - permits authorization of deviations from otherwise applicable current Good Manufacturing Practices requirements

- **REMS Waiver** - expands authority to waive Risk Evaluation & Mitigation Strategies to cover any element based on scenarios giving rise to an emergency use
What is Emergency Use Instructions (EUI)?

- EUI – authorizes the issuance of Emergency Use Instructions for FDA-approved, licensed, or cleared products concerning their approved conditions of use in an emergency or potential emergency.

- Intended to inform:
  - Healthcare providers during emergency
  - Individuals to whom an “eligible product” is to be administered

- Provide information regarding event-driven prevention/treatment of a disease or condition for which the MCM has been approved, licensed, or cleared by FDA in the face of an emergency.

- Facilitate MCM use without violating FD&C Act.

- Provide legal protection for MCM use in a non-medical modality or non-traditional way.
CDC’s EUI Decisional Process

- Identify stockpiled-MCMs that meet the prerequisite criteria
  - FDA-approved, licensed, or cleared **AND**
  - Intended use concerns the MCM’s FDA-approved, licensed, or cleared indication

- Decision to develop and issue EUI will be based on:
  - Emergency use instructions & information that slightly deviate from approved labeling, standard clinical practice, and/or standard medical modality
  - Availability of relevant data/information to assess risk versus benefits
  - Any existing CDC recommendations

- CDC may recommend consideration of an IND/IDE or EUA if emergency use of MCM would present risks for which no data or inadequate information is available to support its use under EUI
Examples of EUI-eligible MCMs:
- Doxycycline and Ciprofloxacin for PEP & treatment of anthrax
- Tamiflu/Relenza for PEP & treatment of acute, uncomplicated influenza; treatment of complicated, hospitalized influenza
- Neupogen for H-ARS with modified dose

Examples of Potentially EUI- or EUA-eligible MCMs:
- Radiogardase for less than 2 years of age
- Anthrax Vaccine for PEP in adults with modified dose or schedule

Examples of EUI-ineligible MCMs (investigational or unapproved use requiring EUA or IND):
- Amoxicillin for PEP and treatment of anthrax
- Anthrax Vaccine for PEP in children
EUI for PEP of Inhalation Anthrax

- **Ciprofloxacin**
  - EUI for Healthcare Providers
  - EUI for Recipients

- **Doxycycline**
  - EUI for Healthcare Providers
  - EUI for Recipients
  - Crushing instructions pamphlet and 1-pager
  - Crushing instructions video ([https://www.youtube.com/watch?v=Wecask69YXw](https://www.youtube.com/watch?v=Wecask69YXw))
Dissemination of CDC Issued-EUI

Before an emergency:
• Documents posted on password-protected CDC JOIN SharePoint for sharing with external public health partners

During an emergency:
• Will be posted on CDC’s public website

Emergency Use Instructions (EUI) for Doxycycline and Ciprofloxacin for Post-exposure Prophylaxis for Anthrax

- CDC-issued doxycycline EUI replace the fact sheets in FDA-issued Emergency Use Authorization
- Also see FDA’s emergency dispensing orders for doxycycline and ciprofloxacin

MCM Information

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<tr>
<th>Type</th>
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<td>Hollingsworth, Susan (CDC/OID/NCEZID)</td>
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</tbody>
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FDA’s Emergency Dispensing Orders

- Emergency dispensing without a prescription
- Dispensing by healthcare providers & non healthcare providers
- Original manufacturers’ packaging or repackaged for emergency dispensing/distribution [UoU, partial supply (10-day)]
- Current good manufacturing practices (cGMP) waiver

In the event of an anthrax emergency, emergency response operations to enable use of oral doxycycline might require transportation, storage, or handling for rapid dispensing without the capability to maintain certain otherwise applicable CGMP conditions during the response. During the period this order is in effect, FDA is hereby permitting temperature excursions that do not exceed 40°C for a total period of less than 7 days during an anthrax emergency response for the shipment and storage of eligible doxycycline products. Products meeting these conditions will not be deemed adulterated or misbranded under the FD&C Act.

http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495126.htm
**Summary Comparison**

**IND**
- Non-emergency or emergency
- No emergency determination/declaration
- Individual recipient or widespread use
- Unapproved MCM or unapproved use of approved MCM

**EUA**
- Emergency or pre-event preparedness
- Emergency/potential emerg. determination + declaration
- Intended for mass MCM use
- Unapproved MCM or unapproved use of approved MCM

**Other Authorities***
- Emergency or pre-event preparedness
- Emergency/potential emerg. determination
- Intended for mass MCM use
- Approved MCM & approved conditions of use

* CDC’s Emergency Use Instructions (EUI) with/without FDA’s emergency use authorities for FDA-approved MCMs
### Summary Comparison, cont.

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<thead>
<tr>
<th>IND</th>
<th>EUA</th>
<th>Other Authorities*</th>
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<tr>
<td>• IRB review/approval</td>
<td>• No IRB review/approval required</td>
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<tr>
<td>• Informed consent</td>
<td>• Includes Fact Sheets</td>
<td>• Includes EUI by CDC</td>
</tr>
<tr>
<td>• Permitted by FDA</td>
<td>• FDA reviews and authorizes</td>
<td>• Other authorities issued by FDA</td>
</tr>
<tr>
<td>• Data collection (AE &amp; outcomes) and reporting</td>
<td>• Conditions per FDA (e.g., record keeping, AE reporting)</td>
<td>• Voluntary safety reporting</td>
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<tr>
<td>• PREP Act applies</td>
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Summary

- FDA-approved
- EUI – Emergency Use Instructions
- IND – Investigational New Drug
- EUA – Emergency Use Authorization
Resources

- FDA Guidance on EUAs and other MCM Emergency Use Authorities (January 13, 2017)

- FDA MCM Emergency Use Authorities Website (official updates, guidance, current actions)

- FDA PAHPRA Questions & Answers (January 2014)
Thank you!

For more information, contact regaffairs@cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.