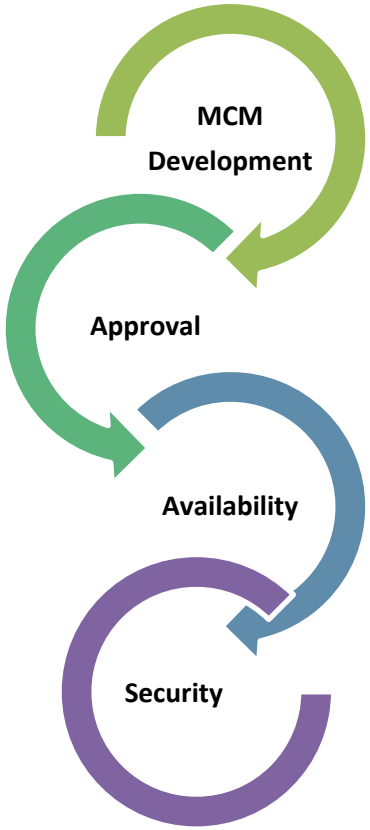
FDA-CDC Joint Learning Session: Regulatory Updates on Use of Medical Countermeasures

Preparedness Summit
August 25–27, 20

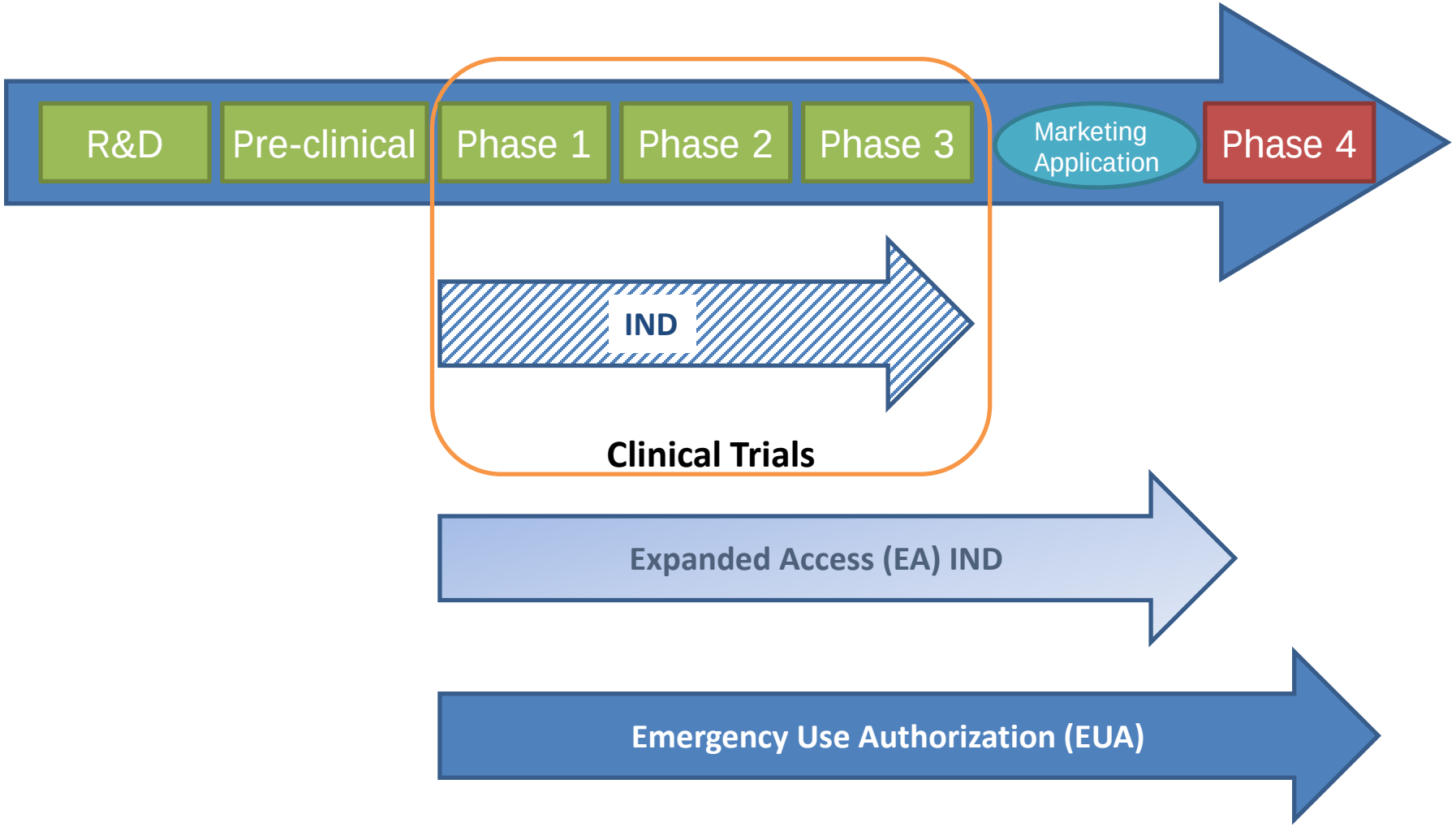
Elizabeth Sadove
Director, Medical Countermeasure Regulatory Policy
Office of Counterterrorism and Emerging Threats
Office of Chief Scientist
Food and Drug Administration

FDA's Public Health Emergency Response

- Facilitating development of MCMs; approving, licensing, clearing, and regulating throughout product lifecycle
- Using legal mechanisms to facilitate emergency use to investigational products
- Preventing shortages
- Protecting blood supply & tissue for transplantation
- Ensuring consumer protection against fraud
- Monitoring MCM use for adverse events to ensure safety and efficacy of FDA-regulated products



Regulatory Mechanisms to Enable Access to Investigational Products



www.fda.gov/medicalcountermeasures

COVID-19 Clinical Trials

- Supporting USG efforts (e.g., OWS, ACTIV) to identify and prioritize candidates and support efforts to obtain data for candidates therapeutics and vaccines with highest potential for clinical use
- Vaccines: Published guidance June 30, “Development and Licensure of Vaccines to Prevent COVID-19,” setting FDA expectations for chemistry, manufacturing and control, nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation
- Established CTAP (Coronavirus Treatment Acceleration Program)
  - As of July 31, 570 + drug development programs are in planning stages and 270 + trials have been reviewed by FDA.
    - For example: 20+ Antivirals; 20+ Cell and Gene Therapies; 30+ Neutralizing Antibodies

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 Federal Food, Drug, and Cosmetic (FD&C) Act:

- Some MCMs needed for a response might not be approved, licensed, or cleared by FDA
- 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 mass dispensed without individual prescriptions, with special instructions, or beyond expiry their dates
- Also, to ensure any available HHS Public Readiness and Emergency Preparedness (PREP) Act protections apply

Legal/Regulatory Mechanisms for Emergency Use of MCMs

- **Expanded Access (EA) to Investigational Drugs and Devices**
  - FD&C Act § 561
  - 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

- **Other Emergency Use Authorities**
  - FD&C Act §§ 564A, 505-1, and 564B
  - Only applicable to FDA-approved MCMs

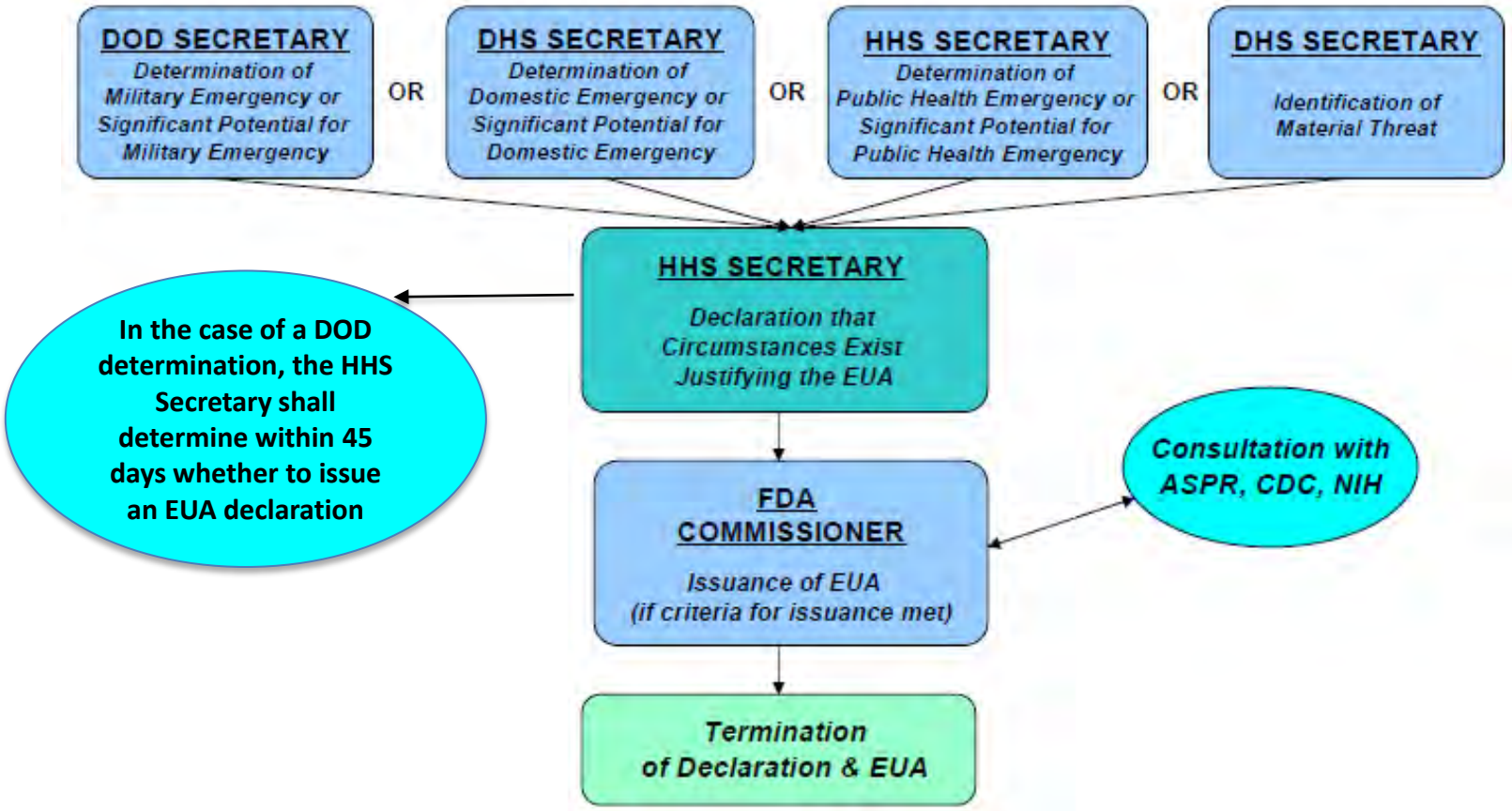
Expanded Access (FD&C § 561)

- Serious or immediately life-threatening disease or condition
- Preserves IND/IDE patient safeguards: Informed consent and Institutional Review Board (IRB) approval
- 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

EUA (FD&C Act § 564)

- For use in emergencies involving CBRN agent(s) (and for DoD, agent(s) of war, FDA can authorize for use to diagnose, prevent, treat:
  - an unapproved medical product or
  - unapproved use of an approved product (e.g., for a new indication), without violating the FD&C Act
- Statutory criteria must be met:
  - Serious or life-threatening disease/condition caused by a CBRN agent(s) referred to in the HHS Secretary EUA declaration
  - Reasonable belief product may be effective
  - Known/potential benefits outweigh known/potential risks
  - No adequate, approved, available alternative to product

Summary of Process for EUA Issuance



EUA Evidence of Effectiveness

- “May be effective”
- Provides a lower level of evidence than the “efficacy” standard FDA uses for product approvals and may not be the same as required for expanded access, IDEs or humanitarian device exemptions
- FDA assesses potential effectiveness of candidate EUA products on a case-by-case basis using a risk/benefit analysis
- 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

No Adequate, Approved, Available Alternative

- "Shortage" EUAs
- EUA guidance: "A potential alternative product may be considered 'unavailable' if there are insufficient supplies of the approved alternative to fully meet the emergency need."
  - Populations, conditions, or circumstances without alternatives
  - Information to support a shortage (e.g., market data, modeling data)

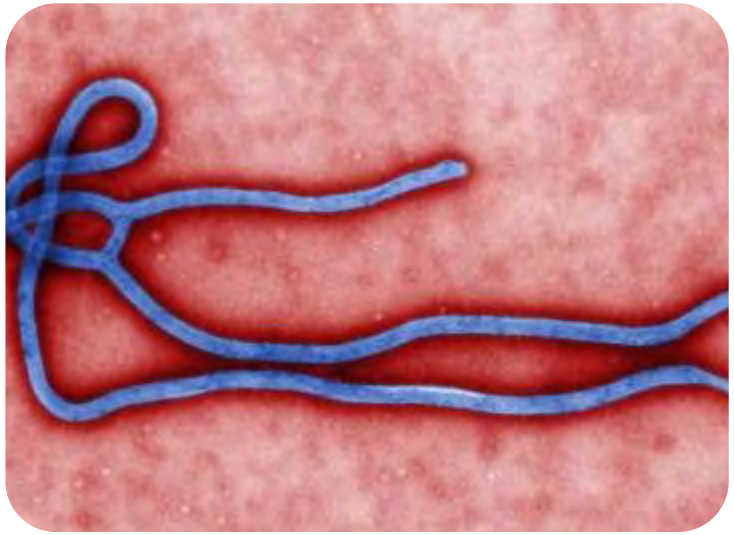
Waivers, Conditions, Priorities

- Allows for case-by-case waivers and flexibilities, e.g., cGMP requirements, Rx requirement
- Conditions of authorization = safeguards, such as:
  - Information on emergency use (e.g., fact sheets for product recipients and for HCPs-including notification the product is not FDA-approved)
  - Dispensing/screening procedures
  - Record keeping and monitoring of adverse events
  - Collection of information
  - Roles (e.g., for DoD, HCPs, laboratories, etc.)
  - Limitations on advertising and promotion
- Prioritization of EUA requests (declinations)—factors may include:
  - Public health need/circumstances of the emergency
  - Product's regulatory status
  - Safety and efficacy data
  - Product quality, shelf life, storage
  - Operational issues

Review, Revocation, Transparency

- Review, Revision, and Revocation
  - FDA must review the circumstances and appropriateness of each authorization
  - FDA may revise or revoke if:
    - The emergency circumstances (i.e., as issued within with the determination) no longer exist
    - The criteria for the issuance of the EUA are no longer met, or
    - Other circumstances make revision or revocation appropriate to protect public health and safety
- Publicly available EUA packages:
  - Consist of:
    - Letter of Authorization
    - Accompanying materials (e.g., fact sheets for health care professionals and patient/recipients, instructions for use, labels)
  - FDA must publish in the Federal Register a notice of each authorization, termination, and revocation
  - FDA posts all of this information real-time on FDA's main EUA website

Pre-COVID-19



- As of December 31, 2019, FDA had 36 Active EUAs (MCMi Fiscal Year 2019 Program Update, Appendix 2)
- Virtually all are for diagnostic tests (i.e., Novel Influenza A (H7N9), MERS-CoV, Ebola, Enterovirus D68, and Zika)
- Atropine Auto-Injectors (2017): Addresses manufacturing issues related to the sole manufacturer of important nerve agent antidotes
- Freeze Dried Plasma (2018): Addresses unique needs of DoD

COVID-19 Device EUAs

- Personal Protective Equipment
  - Respiratory protective devices
  - Surgical masks
  - Face shields, face masks, gowns, barrier protection
  - Decontamination systems for N95s
- Ventilators and accessories, Infusion Pumps, Extracorporeal Blood Purification Devices, Diaphragmatic Stimulators, Remote Monitors, Continuous Renal Replacement Therapy
- Tests
  - As of 8/17, FDA authorized 218 tests
  - 174 molecular tests, 39 antibody (serology) tests, 2 antigen
  - 160 supplements
  - Testing with home collection (plus 2 authorized kits)
  - Testing with pooled samples

Umbrella EUAs

- Novel approaches to enforcement policies and EUAs
- Examples:
  - Ventilators and accessories
  - Gowns and Other Apparel
  - Surgical Masks
  - Face Shields
  - Face Masks
  - 3 different “umbrellas” for RPDs
  - High Complexity Molecular-Based LDTs

COVID-19 Drug EUAs

- Hydrochloroquine & Chloroquine (HCQ & CQ)
  - Issued March 28 to treat certain hospitalized adults & adolescents for whom participation in a clinical trial was not available or participation was not feasible.
    - FDA continually reviews an EUA's appropriateness, including review of emerging scientific evidence from randomized clinical trials.
  - Revoked on June 15, concluding that based on new information, these drugs are unlikely to be effective to treat COVID-19 and that the drugs' potential benefits for such use do not outweigh its known and potential risks.
- Remdesivir
  - Issued on May 1 to treat in-patient, hospitalized adults & children with severe COVID
  - Allocation is coordinated by U.S. government
- To address shortages:
  - Propoven
  - Replacement Solutions used with Renal Therapy devices

Comparison of Access Mechanisms

Consideration	Clinical Trial	Expanded Access (IND/IDE)	EUA
Ability to inform effectiveness	Yes – designed to provide evidence of safety and effectiveness	Not likely; possibly anecdotal information with larger population size	Not likely
Ability to inform safety	Yes – designed to provide evidence of safety and effectiveness	Safety signals might be identified	Safety signals might be identified
Ability to obtain useful information to benefit future patients	Yes - designed and intended to benefit future patients – randomized/blinded	Not likely; with larger sized populations, possibly some safety data in patient subgroups that could inform broader labeling	Not likely
Availability of findings	Eventually published in medical journals. If part of a regulatory approval, FDA makes reviews public.	Individual medical records are not released to the general public. Case reports might be published in medical journals.	Generally there is no systematic data collection. Retrospectives studies may be conducted and published.
Informed consent required?	Yes	Yes	No, but requires informing the volunteer of 1) right to refuse and 2) that product is unapproved/available under an EUA
Institutional review board (IRB) required?	Yes	Yes, but no prior approval needed for individual patient access	No
Level of access to investigational product	Depends on trial design P1 typically 20 – 100 P2 typically several 100 P3 typically 300 – 3,000	Depends on type of expanded access, which ranges from individual patient (e-IND/IDE) to large (e.g., 100-1,000) populations	Can enable access to a large number of patients

Other Emergency Use Authorities

- Section 564A—For emergency use of eligible MCMs that are FDA-approved/cleared for CBRN use, without having to issue an EUA
  - Expiration Dating Extensions
  - Emergency Use Instructions (EUI), delegated to CDC
  - Emergency Dispensing Orders
  - Waiver of cGMPs
- Section 564B—Allows governmental pre-positioning of unapproved products

Lessons Learned?

- 2009 H1N1 Response:
  - Peramavir: CDC performed adverse event monitoring and compliance activities (e.g., follow-up surveys) to ensure timely reporting.
    - "Response rates for MedWatch reporting reminder survey and pharmacy survey were 70% and 73% respectively. Unfortunately only 12% of clinicians contacted through the clinician survey responded."
- "Randomized, controlled, trials are the most reliable way to identify the relative benefits and risks of investigational products, and every effort should be made to implement them during epidemics." (National Academies of Sciences, Engineering, Medicine, "Integrating clinical research into epidemic response: The Ebola Experience," Washington, DC: National Academics Press, 2017.
- 2020 COVID-19 Response, examples:
  - HCQ: As of May 26, BARDA received outcome data for 1,763 patients out of approx. 2.4 million treatment courses distributed to State and local authorities.
    - "Data interpretation is limited due to the low number of patients with reported outcome and the absence of comparison group."
  - Remdesivir: RCT led by the NIH found that helped to reduce the length of hospitalization for COVID-19 patients, with additional trials informing regulatory decisions.
  - RECOVERY Trial: UK-led, enrolling large numbers of patients into a simple trial using a master-protocol approach in which agents can be added or subtracted

For More Information

- **Latest FDA Information on COVID-19 response**
  - **www.fda.gov/coronavirus**
  - FDA's COVID-19 response At-A-Glance Summary: https://www.fda.gov/media/137005/download

- **Expanded Access Website**
  - http://www.fda.gov/newsevents/publichealthfocus/expandedaccesscompassionateuse/default.htm

- **MCM Emergency Use Authorities Website**
  - https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/mcm-emergency-use-authorities
  - https://www.fda.gov/media/136121/download (Appendix 2)


FDA
U.S. FOOD & DRUG
ADMINISTRATION