

CDER's Role in Public Health Emergency Response & Medical Countermeasure Development

FDA Small Business Regulatory Education for Industry (REdI)

July 20, 2021

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Office of the Center Director

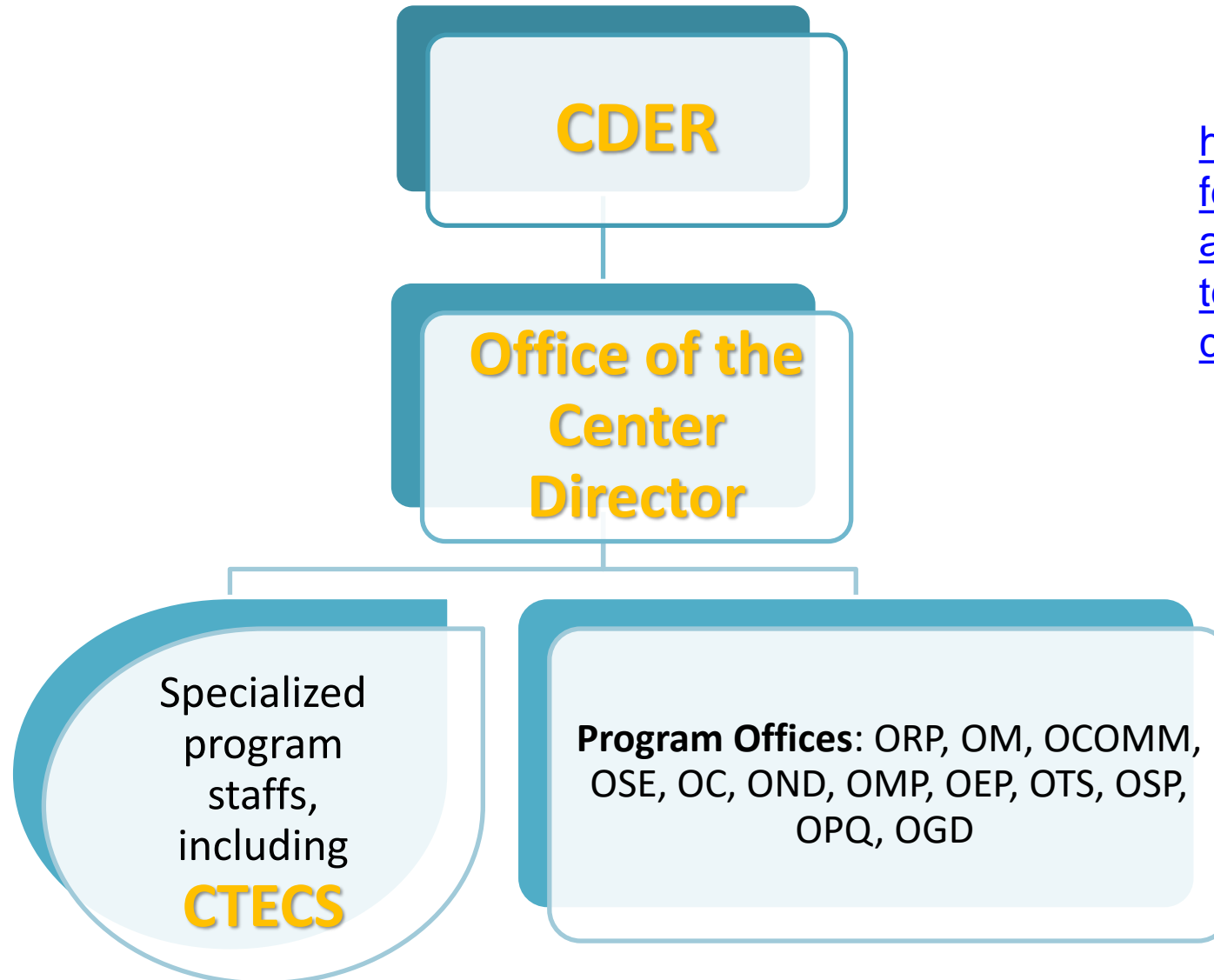
Center for Drug Evaluation and Research (CDER)

U.S. Food and Drug Administration

Learning Objectives

1. Define medical countermeasures (MCMs) and describe MCM development tools
2. Provide an overview of FDA's tools and authorities for facilitating the availability of MCMs for emergency preparedness and response
3. Discuss how CDER approaches response to a potential or actual public health emergency, including for the COVID-19 Pandemic
4. Describe the CDER process for facilitating emergency Investigational New Drug (IND) application requests after-business hours

Counter-Terrorism and Emergency Coordination Staff (CTECS) – Who We Are



About CTECS:

<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/counter-terrorism-and-emergency-coordination-staff-ctecs>

CTECS - What We Do



- Facilitate the development and availability of safe and effective medical countermeasures for chemical, biological, radiological, and nuclear (CBRN) threats and emerging infectious diseases



- Coordinate CDER emergency operations and responses pertaining to drugs and biological therapeutics for CDER-regulated products

What is a Medical Countermeasure (MCM)?

- During public health emergencies, MCMs may be needed to prevent or treat diseases or conditions caused by chemical, biological, radiological, or nuclear (CBRN) or emerging infectious disease threats, like pandemic influenza, Zika virus, and SARS-CoV-2
- FDA is responsible for reviewing the safety and effectiveness of MCMs—including drugs, therapeutic biologics, vaccines, and devices, such as diagnostic tests— to counter these threats

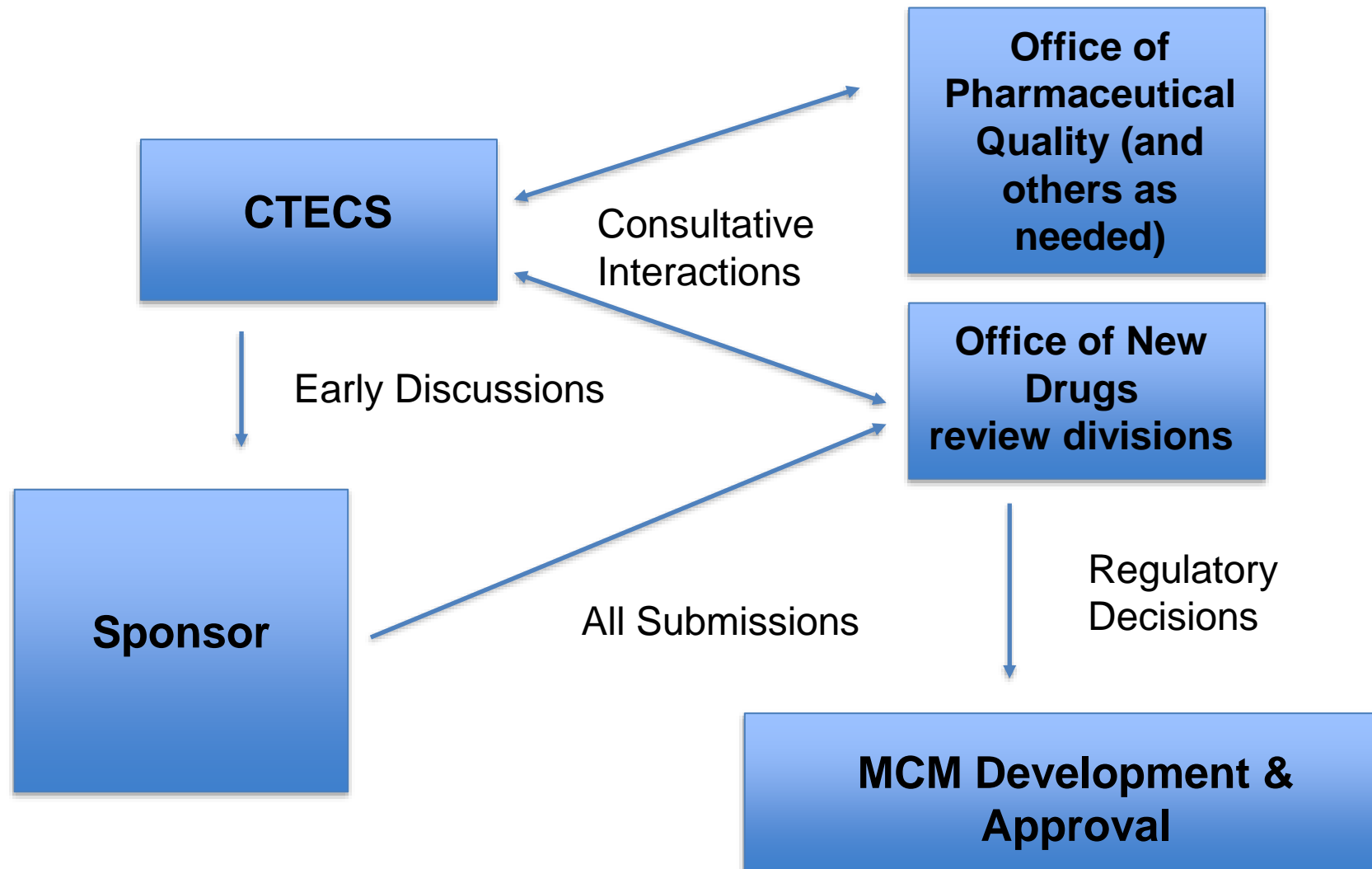
Reference: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/mcm-emergency-use-authorities>

CTECS - What We Do

- Support national emergency preparedness and response needs by liaising with federal and state partners, for example:
 - Assistant Secretary for Preparedness and Response (ASPR)
 - Biomedical Advanced Research and Development Authority (BARDA)
 - Centers for Disease Control and Prevention (CDC)
 - National Institutes of Health (NIH)
 - Department of Defense (DoD)
 - State Departments of Health



CTECS' role as a consultation office within CDER for MCM development





MCM Development

- Most Products Follow the Traditional Development Pathway
 - Animal toxicology
 - Manufacturing quality
 - Human safety and efficacy
- MCM Products are Unique
- “Animal Rule” Pathway
 - 67 FR 37988 (May 2002): **New Drugs; Evidence Needed to Demonstrate Effectiveness When Human Efficacy Studies Are Not Ethical or Feasible**
 - Subpart I: 21 CFR 314.600-314.650 (Drugs)
 - Subpart H: 21 CFR 601.90-601.95 (Biologics)
- FDA Guidance for Industry (Final) – October 2015
 - “**Product Development Under the Animal Rule**”
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf>

Animal Rule



- **Efficacy** is established based on adequate and well-controlled studies in animals
 - “...when the results of those animal studies establish that the drug product *[or the biological product]* is reasonably likely to produce clinical benefit in humans.”
- **Safety** is evaluated under the preexisting requirements for drugs and biological products

Reference: 21 CFR 314.610, 21 CFR 601.91

“Animal Rule” Requirements



[https://www.fda.gov/EmergencyPreparedness/Cou
nterterrorism/MedicalCountermeasures/MCMRegu
latoryScience/ucm391604.htm](https://www.fda.gov/EmergencyPreparedness/Cou
nterterrorism/MedicalCountermeasures/MCMRegu
latoryScience/ucm391604.htm)

- (1) There is a reasonably well-understood pathophysiological **mechanism** of the toxicity of the substance and its prevention or substantial reduction by the product;
- (2) The effect is demonstrated in **more than one animal species** expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans
- (3) **The animal study endpoint is clearly related to the desired benefit in humans**, generally the enhancement of survival or prevention of major morbidity; and
- (4) The data or information on the pharmacokinetics and the pharmacodynamics of the product or other relevant data or information, in animals and humans, allows **selection of an effective dose in humans**.

Reference: 21 CFR 314.610, 21 CFR 601.91

Animal Rule Approvals

- Website: <https://www.fda.gov/drugs/nda-and-bla-approvals/animal-rule-approvals>
- Examples:
 - Tecovirimat (TPOXX) - For the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg
 - Pegfilgrastim (Neulasta) - To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)



Animal Model Qualification Program (AMQP)

- Drug development tool (only for Animal Rule models)
- Model qualification implies that:
 - specific animal species +
 - specific challenge agent +
 - specific route of exposure → produces a disease or condition that corresponds to the human disease or condition of interest
- Animal models
 - Are product-independent
 - Must be replicable
- ***Qualification is a regulatory decision***



What if an MCM is needed for use during a response before it's been approved by FDA?



- Goal: FDA approval before stockpiling and use during a response
- But that is not always possible. For example:
 - There might not be any approved products for the threat or condition
 - An approved product might need to be used in unapproved ways (e.g., in a new age group; for a new threat or condition; without an individual prescription)
 - There might be supply shortages of an approved product
 - Clinical trial environment might not be practical
- **Expanded access mechanisms** (FD&C Act §§ 561, 561A)
 - Investigational New Drug application (IND) (21 CFR 312.300)
- **Emergency use mechanisms**
 - Emergency Use Authorization (EUA) (FD&C Act § 564)
 - Other emergency use authorities (FD&C Act §§ 564A, 564B)



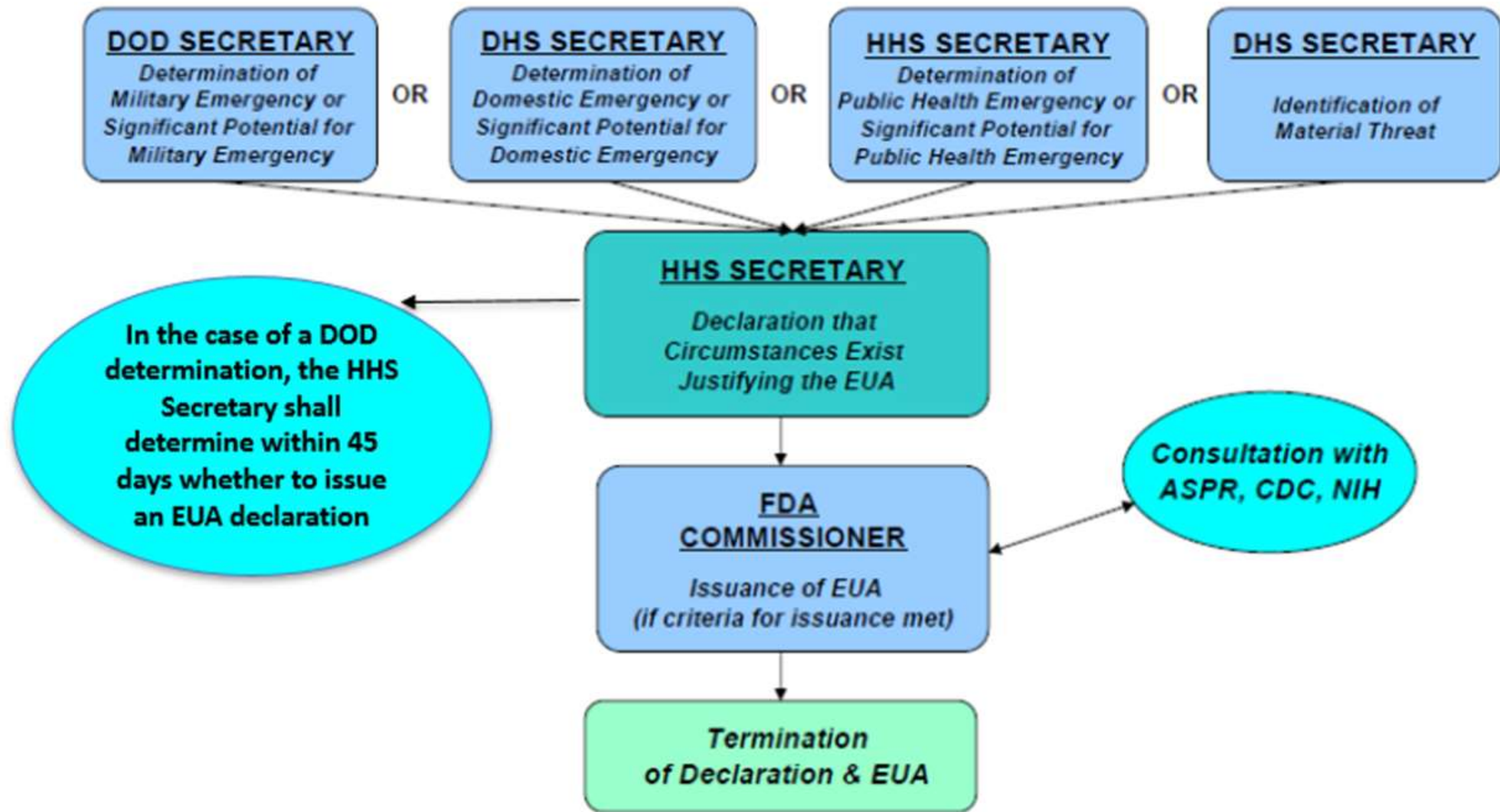
Emergency Use Authorization

- Established by Project BioShield Act of 2004; authority delegated to the Commissioner of Food and Drugs (FDA)
- Amended by:
 - PAHPRA (2013) (to provide additional pre-event flexibilities)
 - 21st Century Cures Act (2016) (to add animal drugs)
 - P.L. 115-92 (2017) (to provide additional flexibilities for DoD)
- Part of the post-9/11 Federal Government focus on MCM stockpiling and preparedness for counterterrorism
 - Provided physicians and public health officials an “important new tool” for public health and medical care under emergency conditions
- Recognition there will always be promising new drugs, biological products, and devices in the pipeline, as well as promising investigational uses

Emergency Use Authorization (EUA)

- What is an EUA?
 - A legal mechanism FDA can use to facilitate access to critical medical products during certain defined emergency events
- With an EUA, FDA can authorize for use in emergencies involving a CBRN agent(s) [and, for DoD, an agent or agents that may cause, or are otherwise associated with, an imminently life-threatening and specific risk to United States military forces] the:
 - Use of unapproved MCMs
 - or
 - Unapproved use of approved MCMs (e.g., for a new indication, such as amoxicillin for anthrax)
- FDA EUA page: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>
- FDA EUA guidance: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>

Summary of Issuance Process for an EUA



COVID-19 Response and EUA Examples



- **2/4/20: HHS issued an EUA determination**
 - Pursuant to Section 564(b)(1)(C) of the FD&C Act, the Secretary of HHS determined that there is 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 virus that causes COVID-19
- **3/27/20: HHS issued an EUA declaration for drugs and biological products**
 - On the basis of the 2/4/20 HHS EUA determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the FD&C Act, subject to terms of any authorization issued under that section
- **CDER COVID-19 EUAs: 9 EUAs for products to treat COVID-19 and serious conditions caused by COVID-19**
 - One treatment (remdesivir) is currently approved by the FDA for use in COVID-19
 - Remdesivir, monoclonal antibodies, supportive care (intubation, dialysis)
- **Other COVID-19 EUA examples:** vaccines, convalescent plasma, testing devices, PPE, decon systems, ventilators, infusion pumps

EUA Criteria for Issuance

- Serious or life-threatening illness/condition caused by the agent(s) referred to in the HHS Secretary's EUA declaration
- Based on the totality of scientific evidence available to FDA, there is a reasonable belief the product
 - “may be effective” in preventing, diagnosing, or treating serious or life-threatening diseases or conditions caused by the agent(s)
 - Known/potential benefits outweigh known/potential risks
 - Provides for a different standard of evidence than for product approvals
 - Case-by-case review: Recommended safety and effectiveness data requirement can vary depending on the nature of the emergency and product candidate
- No adequate, approved, and available alternative to the product



EUA Conditions of Authorization

- Safeguards specific to each EUA (some are required, some are discretionary to protect the public)
- Found within the EUA's Letter of Authorization
- May include
 - Adverse event reporting requirements
 - Manufacturing and distribution requirements (e.g., cold chain)
 - Labeling requirements

EUA Fact Sheets



- Fact Sheet for Healthcare Providers
 - Information comparable to an FDA-approved package insert or instructions for use
 - Serves as labeling resource during emergency response
 - Approved product authorized for unapproved use can refer to Package Insert
- Fact Sheet for Patients or Parents/Caregivers
 - May include patient info, such as side effects, storage, contraindications
- Try to be mindful of length for emergency response logistics
 - For example, printing and making available at Points of Dispensing (PODs)

FDA Review of EUA Requests

- FDA review timelines and action on an EUA request depend on:
 - The product profile – What product data are available to support a risk/benefit analysis?
 - The existence, if any, of pending applications (i.e., IND, pre-EUA) for the product – What does FDA already know about the product?
 - The nature of the emergency – How imminent is the threat?
 - Other relevant factors – Product data in related disease states, safety information?
- Although the time required for FDA action will vary, in an emergency situation that is occurring or believed imminent, a request for consideration for an EUA could be acted upon by FDA within a matter of hours or days



Other MCM Emergency Access Authorities

- During emergency responses, certain uses of approved medical products may be needed to achieve critical public health goals, but could violate provisions of the FD&C Act, for example:
 - Dispensing a drug product beyond its labeled expiration date
 - Giving recipients a simplified fact sheet about the product that are not part of its FDA-approved labeling
- Section 564A of the FD&C Act (PAHPRA, 2013)
 - Emergency dispensing orders
 - Emergency use instructions
 - Expiry dating extensions
 - Waivers of certain CGMP and REMS requirements

Emergency Coordination of Public Health Issues in CDER



What does “emergency” mean to CDER?



- Extreme weather
- Drug product quality issues
 - Contaminated drugs
 - Suspected tampering or counterfeiting
- Acute supply shortages
- Emerging infectious disease
- Patient access to INDs



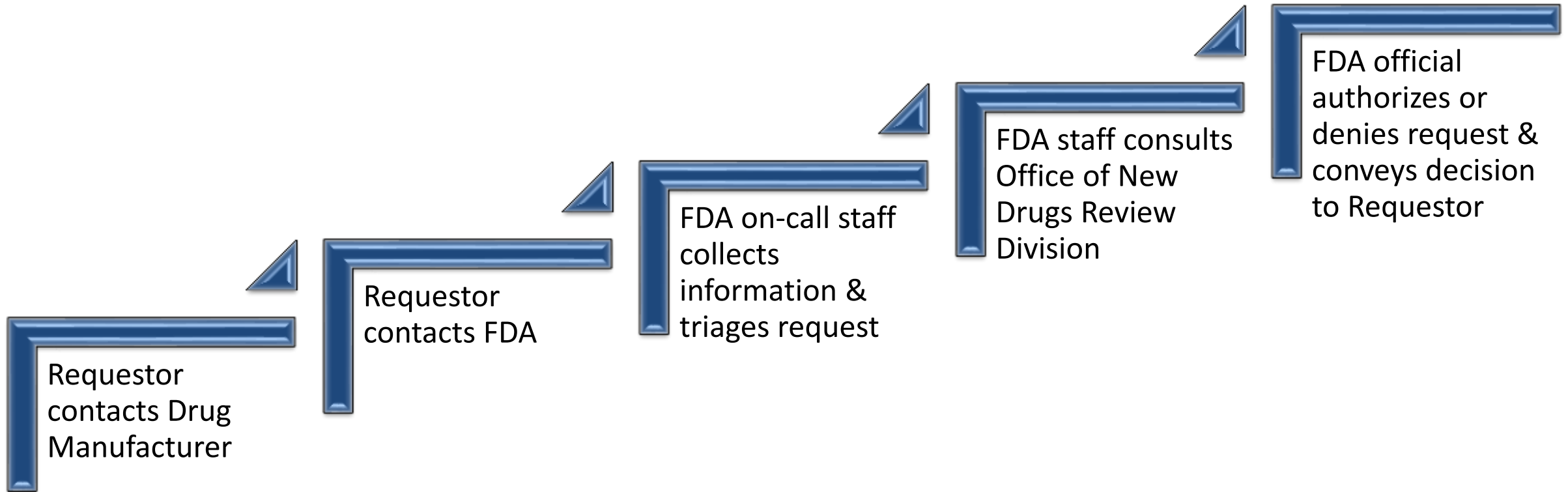
Emergency Investigational New Drugs (EINDs)



- Expanded Access Program (21 CFR 312.300) – “Compassionate Use”
- INDs, “Emergency Procedures” (21 CFR 312.310(d) – emergent use of investigational drug that does not allow time for submission of an IND in accordance with 21 CFR 312.300
 - Individual patient requirement



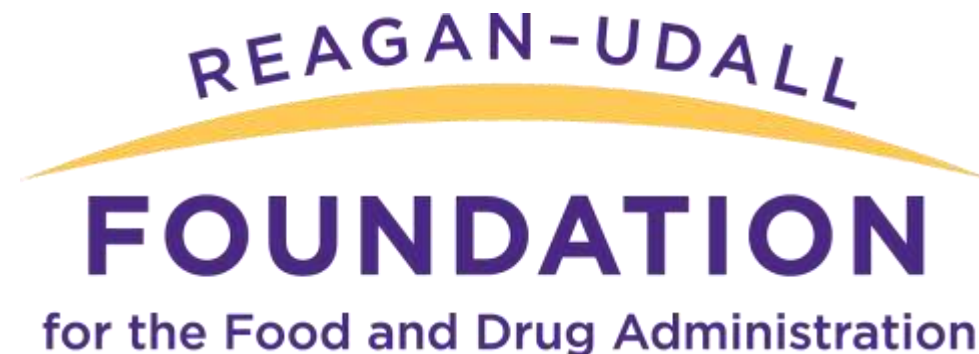
After-Hours EIND Request Process



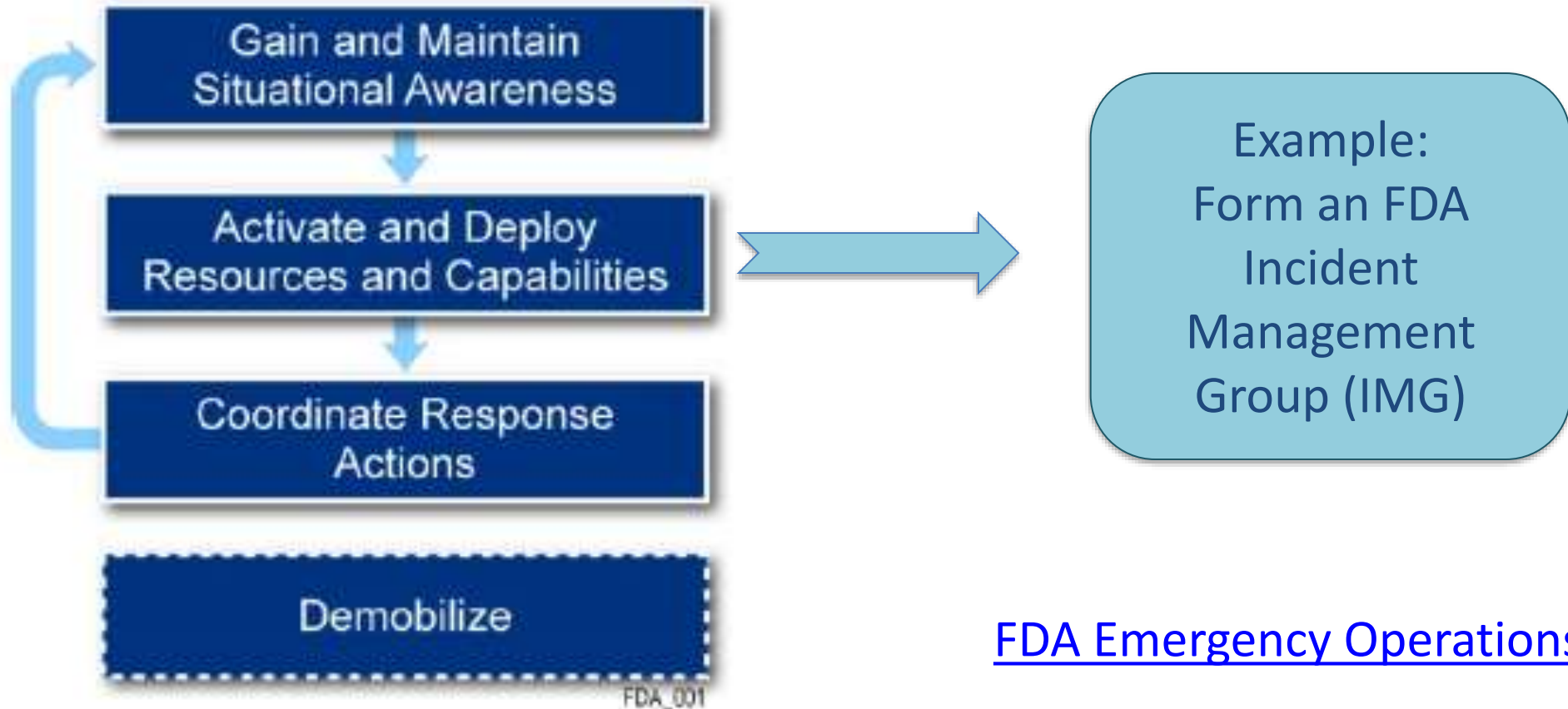
Pandemic adaptation: COVID EIND Call Center

EIND Tools & Resources

- FDA
 - Website: [FDA Expanded Access Webpage for Industry](#)
 - Form 3926 – Individual Patient Expanded Access (EA) IND
 - Guidance for Industry
 - [Individual Patient EA Applications: Form FDA 3926](#)
 - [EA to Investigational Drugs for Treatment Use - Qs and As](#)
- Reagan – Udall Foundation’s Expanded Access Navigator



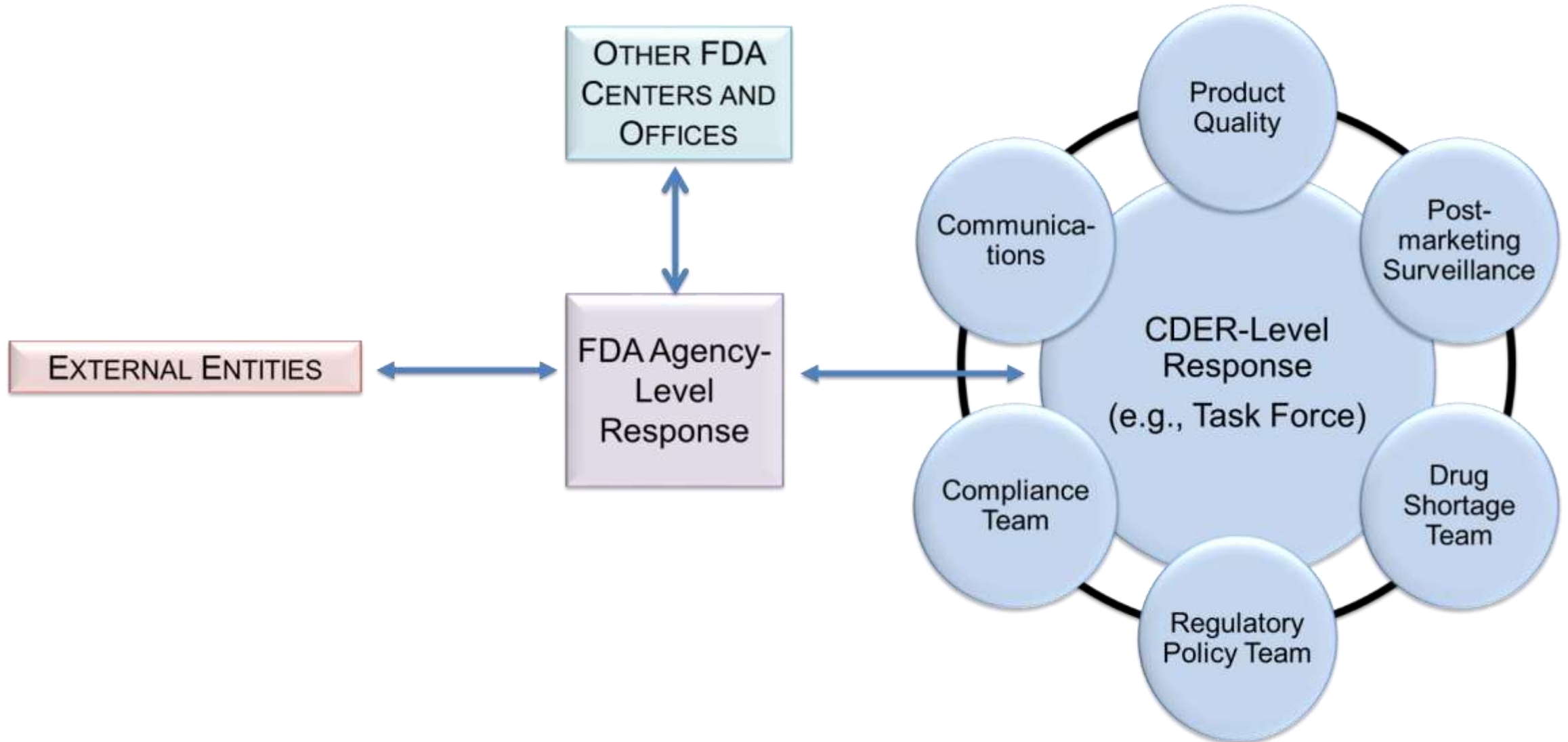
Public Health Emergency Response – FDA Emergency Operations Plan



[FDA Emergency Operations Plan](#)

1. FDA Emergency Response Elements

Public Health Emergency Response – Example CDER Framework



CDER Emergency Response Activities

- Assemble Subject Matter Experts (SMEs)
- Establish USG partnerships
- Collect information & data
- Perform FDA inspections
- Utilize FDA testing capabilities
- Establish communication mechanisms
- Determine appropriate regulatory actions
- Develop strategic response

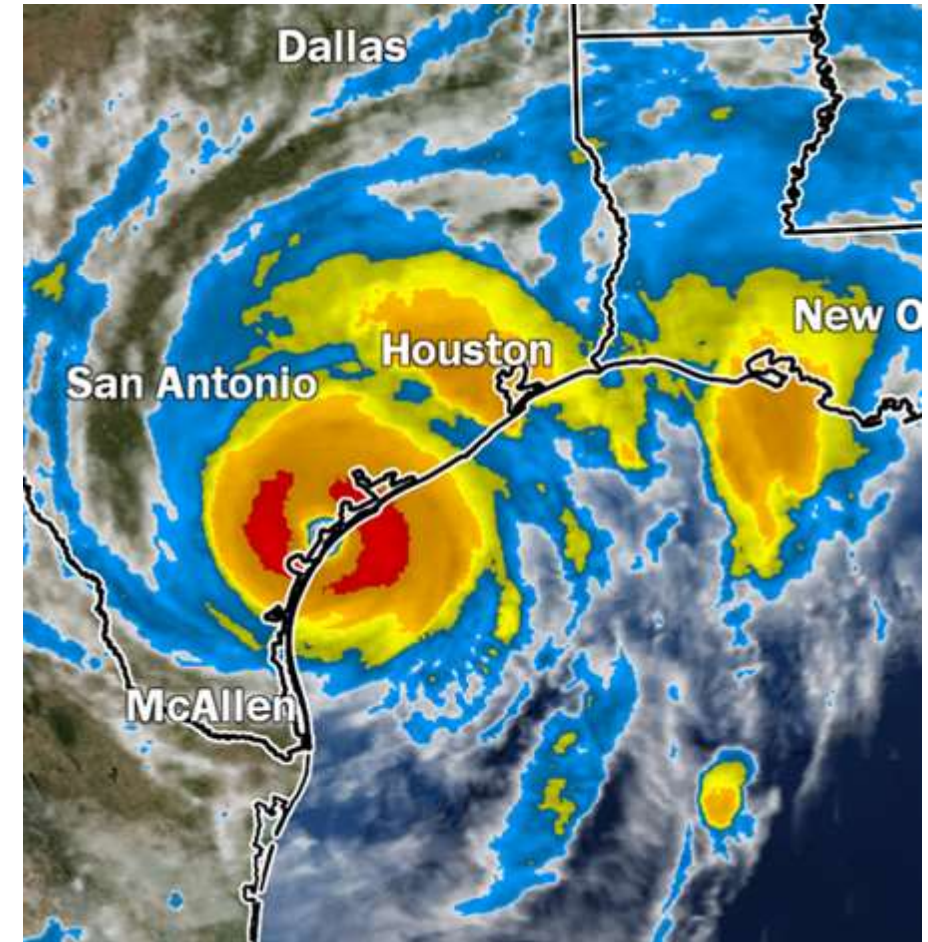
CDER Incident Management Plan



CDER Emergency Scenario: Natural Disaster

Key Objectives:

- Confirm CDER staff safety
- Ensure potentially contaminated CDER-regulated products are not introduced into commerce
- Prevent / mitigate product shortages



CDER Emergency Scenario: Product Issue Concern



Definition of an Adulterated Drug – 21 USC 351

Key Response Objectives:

- Protect public health by ensuring the **safety, quality, and security** of human drugs
- Communicate response findings to stakeholders

Example:

- Liquid docusate sodium contaminated with *Burkholderia cepacia*

CDER Emergency Scenario: Product Issue Concern



Example:

- Hand sanitizer (HS) adulterated with methanol

HS is regulated by FDA as an OTC drug*:
“consumer antiseptic rubs”



*EPA is responsible for regulating hard surface cleaners

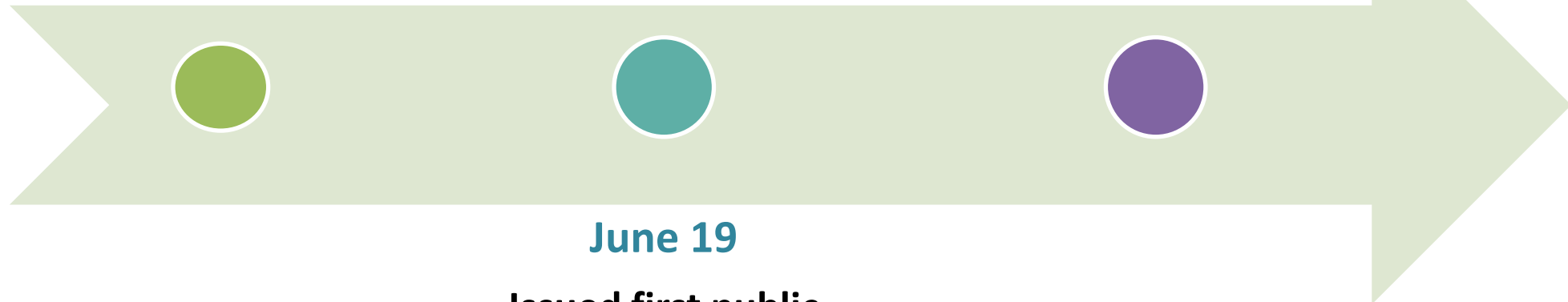
Hand Sanitizer (HS) – FDA Response Timeline

June 2020

FDA became aware
of increased reports
of methanol
poisoning associated
w/ HS

July 27 – Placed certain
HS on Import Alert;
created list of HS that
consumers should not use

July 31 – Warned against
subpotent HS



June 19

Issued first public
warning

July 2

Updated public
warning

Hand Sanitizer (HS) – FDA Response Timeline

August 12, 2020

Added warning for 1-propanol contamination

August 24

Provided impurity testing method



January 21, 2021

Provided policy for testing alcohols used in drug manufacturing for the presence of methanol

August 27

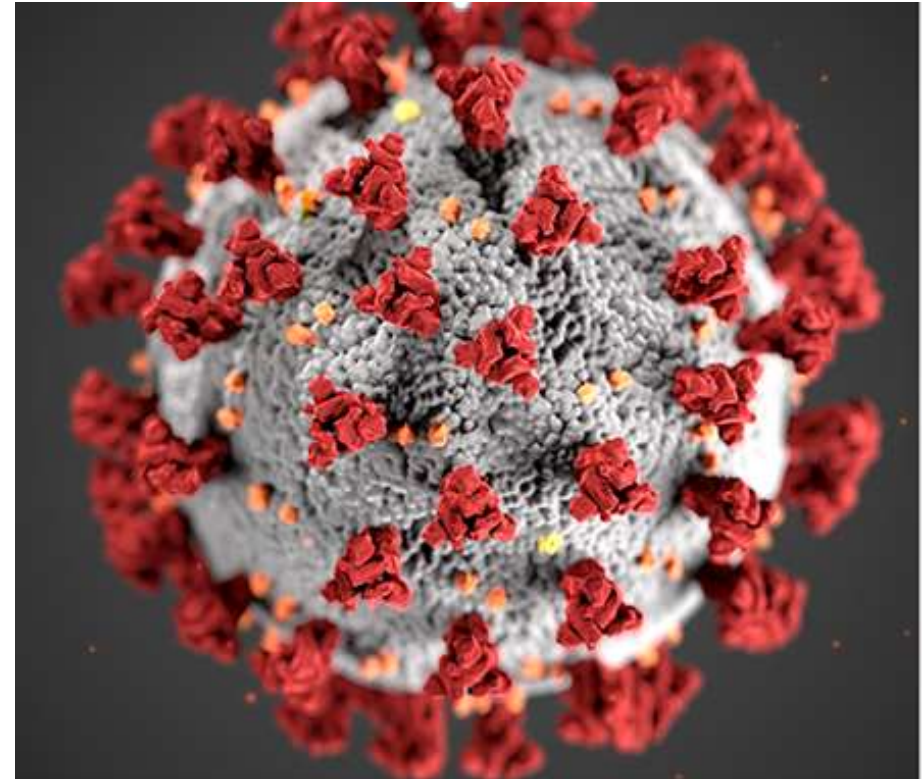
Issued warning for HS packaged in food and drink containers

January 26, 2021

Placed all alcohol-based HS from Mexico on Import Alert

Critical COVID Response Activities

- Global supply chain
- Fraudulent drug products
- Drug development
- Pharmacovigilance
- Inspections
- Public communications



COVID & Drug Supply Chain



Drug Shortages – Proactive Monitoring, Prevention, & Mitigation

What FDA CAN require:

- Notification by manufacturers
 - Supply disruptions
 - Delays
 - Discontinuations
- Notification of manufacturing changes

What FDA CANNOT require:

- A company to make a drug
- A company to make more of a drug
- How much and to whom the drug is allocated

COVID-related Drug Shortage Resources



1) FDA Drug Shortage website

<https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>

Search Extended Use Dates

2) [FDA COVID-19-Related Guidance for Industry](#)

(topics include 503A & 503B facility compounding, ethanol API & hand sanitizer preparation, ANDAs, glass vials/stoppers, resuming normal manufacturing operations, etc.)

COVID & Fraudulent Products



- **Fraudulent products** claim to prevent, treat, or cure diseases or other health conditions, but are not proven safe and effective for those uses
- **FDA Operation “Quack Hack”**
- [FDA Fraudulent Product Flickr Photo Album Link](#)
- [FDA COVID-19 Fraudulent Product Webpage](#)

Report Unlawful Products:

<https://www.accessdata.fda.gov/scripts/email/oc/buyonline/english.cfm>

COVID & Fraudulent Products

FDA Actions

- Warning Letters
 - Since March 2020,
 - 16* Warning Letters issued to internet pharmacies
 - 119* Warning Letters issued to manufacturers of products with drug claims
- Seizures
- Injunctions



Case Example: “Miracle Mineral Solution”



- April 8, 2020: issued Warning Letter (WL) to Genesis II Church of Health & Healing
- April 17, 2020: federal court entered a temporary injunction
- July 9 and August 3, 2020: permanent injunctions entered

Critical COVID Response Activities

- Drug development
 - Example: Coronavirus Treatment Acceleration Program
- Pharmacovigilance
 - Example: COVID-19 EUA FAERS Public Dashboard
- Inspections
 - Example: Guidance for Industry on “Remote Interactive Evaluations” ([Guidance Link](#))
- Public communications
 - Example: Numerous FDA.gov webpages, social media postings, Press Releases, media outreach, etc.

Summary

Summary

- CDER's mission to ensure the efficacy, safety, and security of human drugs continues during the COVID-19 pandemic
- MCM development programs and emergency access authorities are a critical component of emergency preparedness and response efforts
- CDER has established, yet flexible, emergency response procedures and authorities that are utilized in all types of public health emergency situations
- CDER provides 24/7 support to facilitate patient access to emergency use of investigational new drugs

Challenge Question 1



FDA's issuance of an EUA means the product is FDA-approved.



Challenge Question 2



Which of the following is NOT an example of a public health intervention employed by the FDA during the COVID-19 pandemic?

- a. Removing fraudulent products that claim to kill SARS-CoV-2 on hard surfaces from the consumer marketplace.
- b. Placing firms manufacturing adulterated hand sanitizers on FDA Import Alert.
- c. Reviewing product stability data submitted by drug manufacturers to determine if extensions of labeled expiration dates are scientifically supported.
- d. Publishing temporary policy under which outsourcing facilities can compound certain critical care drugs that are not on the FDA Drug Shortage List.

Questions



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