

# Kansas Department of Health and Environment

## EUA and IND for Medical Countermeasures

### Information for State and Local Health Officers

#### I. What is Emergency Use Authorization (EUA)?

An Emergency Use Authorization (EUA) is a critical new tool for the medical and public health communities and is applicable for both civilian and military use. It fills the need for timely and practical medical treatment when the relevant product has NOT already been approved or approved for this specific use by the US Food and Drug Administration (FDA). An understanding of this new product category and its implementation is important to those who will be on the frontlines providing direct care, as well as to those who will be managing mass care situations.

- ❖ **Types of Products: Drugs, Biologics, and Medical Devices**
- ❖ **Product Classification: Unapproved product or unapproved use of an approved product**

#### How does this relate to the practice of medicine?

- FDA generally does not regulate the practice of medicine
- Once a product is approved or cleared, a licensed health care professional has the freedom to use that product for any purpose, even if the use is inconsistent with the product's approved labeling
- Even in the midst of a public health emergency, FDA does not regulate the practice of medicine
- However, to protect the public's health, FDA and the courts are very strict in preventing marketers from promoting products for uses for which they are not approved or cleared by FDA
- The concept of "intended use" is central to FDA enforcement efforts with respect to most of the products it regulates. For example,
  - An apricot pit is a drug if it is intended for the treatment of cancer.
  - A drug is misbranded and illegally marketed if it is labeled for one use and intended for another use.

#### As a local health officer, what should I know about EUAs?

- Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act), amended by the Project BioShield Act of 2004, permits authorization of such products for use in diagnosing, treating, or preventing serious or life-threatening diseases or conditions caused by biological, chemical, radiological, or nuclear agents, if certain statutory criteria are met.
- Typically, FDA receives requests for EUAs from federal partners (e.g., CDC) or from product manufacturers
- HHS Secretary needs to declare an emergency for an EUA to be used
- FDA Commissioner issues the EUA with criteria/conditions that must be applied (see page 3)

- Use under an EUA is not investigational, so Institutional Review Board (IRB) approval and informed consent are not required; alternative dispensing mechanisms can be authorized (Note: EUA does not eliminate the need for Investigational New Drug (IND))

## II. What is an Investigational New Drug (IND) Application?

FDA regulations permit the use of investigational drugs for serious or life-threatening diseases or conditions in certain circumstances. Investigational New Drug (IND) allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.233 or Sec. 312.34.4 It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

### What types of IND applications are there?

During an emergency, IND authority may be an appropriate mechanism for use of an unapproved product (drugs, biologics, and medical devices) or the use of an approved product for a new, unapproved use. This also applies to Investigational Device Exemption (IDE).

- 1) Emergency use IND
  - Individual/single patient access for a serious disease
- 2) Expanded access trial under an IND
  - Intermediate-sized patient populations
- 3) Treatment use IND
  - Widespread access

### What does an IND application require?

Requires patient safeguards, including in most cases:

- 1) Informed consent by subjects
- 2) Institutional Review Board (IRB) supervision
- 3) Reporting to FDA, including outcome collection on safety and efficacy

### What is the difference between EUA and IND/IDE?

Regulatory Requirement	EUA	IND / IDE
	Delivery of medical products for treatment/prophylaxis of the affected population in an emergency	Assess the safety of a medical product and assure human subject protection in a clinical
Investigational Review Board	Not Required	Required 21 CFR part 56
Written/Witnessed Informed Consent	Not Required	Required 21 CFR part 50
Protocol Training	Not Required	Required
Adverse Event Monitoring/Reporting	May be required	Required
Recordkeeping/Access	May be required	Required
Duration	Up to one year	Length of clinical trail

### III. What are Medical Countermeasures (MCMs) and Project BioShield?

Medical countermeasures (MCMs) are the drugs, vaccines, and medical devices used to mitigate or prevent the human health effects of chemical, biological, radiological, or nuclear (CBRN) emergencies (e.g., an anthrax attack or influenza pandemic).

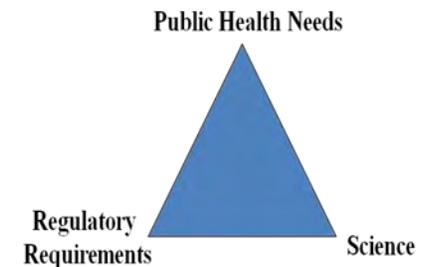
Project BioShield is a comprehensive effort to develop and make available modern, effective drugs and vaccines to protect against attack by biological and chemical weapons or other dangerous pathogens. The objective is to:

- ❖ Strengthen National Institutes of Health (NIH) development capabilities by speeding research and development
- ❖ Give FDA the ability to make promising treatments quickly available in emergency situations
- ❖ Provides for emergency use of “investigational” medical products not yet approved, licensed or cleared by the FDA

#### Why would MCMs need an EUA?

- Lessons learned from the 2001 Anthrax
- Investigational Review Boards not practicable during a rapidly progressive public health emergency
- Informed consent process may limit public health’s ability to respond and contain the disease/outbreak
- Novel/investigational products may be the best available products to meet the needs of a particular emergency
- Requirements for clinical investigations or expanded access would be difficult to meet in emergency mass dispensing or mass vaccination scenarios
- Potential gap exists for Public Readiness and Emergency Preparedness (PREP) Act liability coverage
- Changes from FDA-approved labeling, expiration dating, dosing schedules, and prescribing requirements would render the product misbranded or unapproved under FDA law

#### FDA’s Medical Countermeasure (MCM) Balance



Type of MCM	Authorization
Some MCMs are intended to be used consistent with their approved labeling. →	There is no need for further review/authorization.
Some MCMs are intended to be used in ways beyond their FDA-approved labeling. →	Special legal/regulatory approaches are needed (e.g. without a prescription, in different dosing regimens)
Some MCMs are not yet FDA-approved for any use, but might be helpful for an emergency response because of the lack of other suitable alternatives. →	Special legal/regulatory approaches are needed
<b>Legal dispensing of Strategic National Stockpile MCMs to patients may not occur until the EUA is authorized for the appropriate assets.</b>	

CDC IND Protocols for SNS Products (Cat A Threat Agents)			
Agent	Treatment	Prophylaxis	Vaccine
Anthrax	Cipro* Doxy Penicillin Clindamycin* Rifampin* Vancomycin* <b>AIG*</b> <b>ABthrax*</b>	Cipro Doxy Amoxicillin*	BioThrax Pre-exposure <b>BioThrax Post-exposure*</b> <b>(3 doses + abx)</b>
Plague	Cipro* Doxy <b>Gent*</b>	<b>Cipro*</b> Doxy	NONE
Tularemia	Cipro* Doxy <b>Gent*</b>	<b>Cipro*</b> Doxy	NONE
Smallpox	Treatment of adverse reactions to vaccine: VIG <b>Cidofovir*</b>	NONE	Acambis <b>Aventis Pasteur*</b> <b>MVA*</b>
Botulism	Antitoxin Type: <b>Heptavalent* A*</b>	NONE	NONE
*Indicates drug is not FDA approved for the agent Indicates drug is subject to use under a CDC IND protocol			

#### IV. How does EUA Request and FDA Issuance occur?

During an emergency, the risk-benefit analysis may change. Processing occurs on a case by case basis. If FDA grants an EUA request, it is finding that—during a particular type of emergency— the EUA’s conditions are observed:

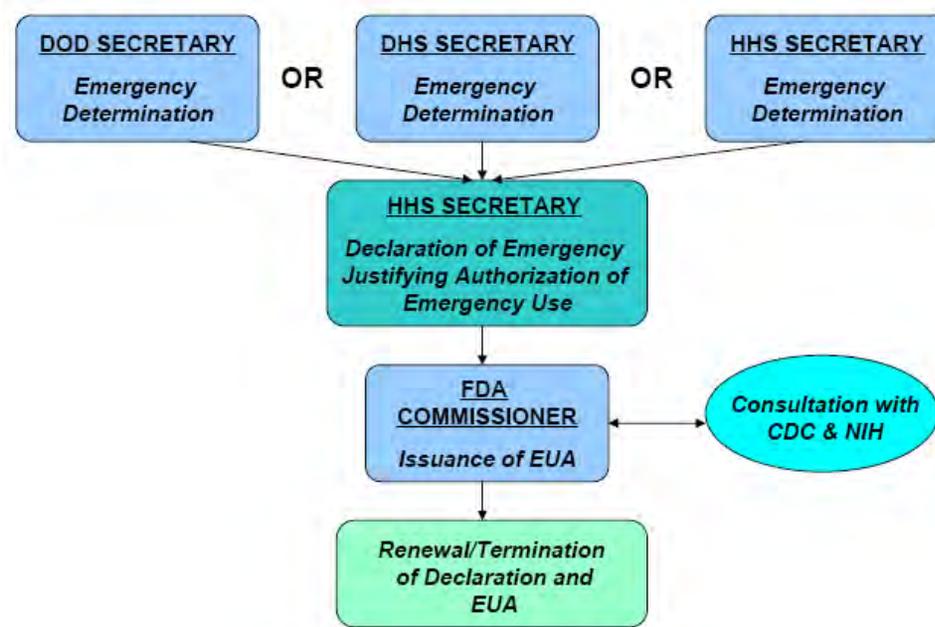
- ❖ An FDA-approved product may be used in a way inconsistent with the limitations of the approval, or
- ❖ A product that has not yet been approved by FDA may be permitted to be used despite lacking the quantum of data that would be necessary for a full approval.

## What factors does FDA consider?

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- 1) That the agent specified in the declaration of emergency can cause a serious or life-threatening disease or condition
- 2) That, based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product MAY BE effective in diagnosis, treatment, prevention
  - The serious or life threatening disease or condition, or
  - A serious or life-threatening disease or condition caused by a product authorized under section 564, or approved, cleared, or licensed under the Act or PHS Act, for diagnosing, treating, or preventing the disease or condition referred to in paragraph (1) and caused by the agent specified in the declaration of emergency
- 3) That the known and potential benefits of the product outweigh the known and potential risks of the product when used to diagnose, prevent, or treat the serious or life threatening disease or condition that is the subject of the declaration
- 4) That there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such serious or life threatening disease or condition
- 5) Other factors that may be considered:
  - Circumstances of the emergency
  - Public health need
  - Product Quality, Shelf Life, Storage
  - Timeliness of product distribution
  - Dispensing/screening procedures (e.g. dispensed post-event or pre-event, dispensed by non-licensed volunteers)
  - Information to be provided on the emergency use (e.g., fact sheets for recipients)
  - Monitoring of adverse events; waiver of CGMP requirements; etc.

Step	Required action	Responsible authority
1	Determination of an emergency justifying issuance of an EUA	Secretary of Homeland Security determines there is a domestic emergency OR Secretary of Defense determines there is a military emergency OR Secretary of Health and Human Services determines there is a public health emergency
2	Declaration of emergency	Secretary of Health and Human Services
3	Consultation (to the extent feasible) between the FDA, NIH, and Centers for Disease Control and Prevention (CDC)	FDA commissioner, NIH director, CDC director
4	Issuance of an EUA	FDA commissioner (under delegated authority from Secretary of Health and Human Services)



## V. Other EUA Information

### EUA Revocation

- Occurs when criteria of issuance are no longer met or as necessary to protect public health or safety

### EUA Termination

- Duration of EUA is a maximum of one (1) year, Length of the declared emergency

### EUAs Issued to Date

- Department of Defense (anthrax vaccine) (2005) (terminated)
- H1N1 Influenza Pandemic (2009) (terminated)
  - Drugs (antivirals—multiple EUAs)
  - Devices (IVDs—multiple EUAs)
  - Personal protective equipment (PPE)
- Mass Dispensing (doxycycline) (2011) (current)
- National Postal Model (doxycycline home and workplace kits for eligible USPS employee volunteers and family members) (2011) (current)

### Pre-EUA activities

- Pre-EUA activities are ongoing between CDC and FDA for SNS assets. This also covers SNS assets that have been tested under the Shelf Life Extension Program (SLEP), under which expiration dates may be extended.

### What does a PREP Act declarations provide related to this?

- The Public Readiness and Emergency Preparedness Act (PREP) provides compensation to individuals for serious physical injuries or deaths from pandemic, epidemic, or security countermeasures identified in a declaration issued by the Secretary pursuant to section 319F-3(b) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d-6d).
- If a person is given a countermeasure (such as a drug under an EUA) that is authorized for emergency use in a declaration made by the HHS Secretary, that person may be eligible for compensation for covered serious physical injury or death from the countermeasure under PREP. For more information on the PREP Act and for information on filing a request for benefits, visit the HRSA Website <http://www.hrsa.gov/countermeasurescomp/> or <http://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx>
- If the FDA issues an EUA to allow for the lawful distribution or dispensing of products for emergency use under certain circumstances and states do not distribute or dispense the countermeasures in accordance with the scope and conditions of the EUA, liability protections afforded by the PREP Act may be affected. In addition, non-SNS assets can be used before SNS assets arrive, but if they are not used under EUA or strictly in accordance with the drugs' approval, then PREP Act liability immunity protections may not be in effect.

## VI. What are the Conditions of Authorization?

*For unapproved products, the law requires the FDA Commissioner (to the extent practicable given the circumstances of the emergency) to establish certain conditions on an EUA that the Commissioner finds necessary or appropriate to protect the public health, and permits the Commissioner to establish other conditions that he finds necessary or appropriate to protect the public health. Such conditions may include a requirement to disseminate information to health care providers or authorized dispensers and prospective patients and other consumers regarding the EUA, the product's significant known and potential benefits and risks and the extent to which such benefits and risks are unknown; available alternatives and their benefits and risks; and, for prospective patients and consumers, the option to accept or refuse the product and any consequences of refusal. Other conditions may include adverse event reporting and monitoring, data collection and analysis, and recordkeeping and records access. For unapproved uses of approved products, certain of these conditions and other conditions may be required in an EUA. Use of a product under an authorization must be consistent with any conditions imposed on the EUA.*

### Examples of EUA conditions:

Any EUA issued will likely impose some conditions at the time of the authorization that must be followed. These conditions will be outlined in FDA's EUA at the time of the event. EUA is published in Federal Register and posted on FDA website after issuance. The following are examples of the potential conditions, but FDA could impose other conditions or different conditions:

#### *FACT SHEETS: Must provide authorized health care provider and recipient fact sheets*

- FDA Fact Sheet example for the Health Care Provider or Authorized Dispenser and for the Recipient <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm>
- To be legally distributed, fact sheets distributed to recipients and health care providers receiving SNS assets MUST be authorized under the EUA. It will be the state or local's responsibility to provide copies of EUA-authorized fact sheets to health care providers and recipients receiving SNS assets.
- EUA doxycycline and ciprofloxacin fact sheets will now be provided by the federal government. These fact sheets cannot be finalized until the EUA is authorized (at the time of an event). The duration of therapy for post-exposure prophylaxis (PEP) for inhalation anthrax in the FDA-approved labeling for ciprofloxacin and doxycycline is 60 days. CDC's pre-EUA submission proposes that additional written information be distributed regarding the dispensing of a 10-day supply of doxycycline and ciprofloxacin as well as written information regarding the remaining course of treatment, if needed, as part of a mass dispensing strategy. Fact sheet information on the partial 10-day supply is outside the scope of the approved drug applications (where the prophylaxis course is described as 60 days). The only written information that can be legally distributed is that approved as part of the drug applications or that authorized under an EUA that might be issued.
- It is possible that FDA could make changes to the fact sheets as part of any EUA that might be issued if, for example, new information with respect to risks and benefits became available prior to issuance of the EUA. CDC has submitted a pre-EUA submission with proposed fact sheets for FDA review. CDC and FDA are coordinating closely to limit to the extent possible the need for last minute changes.

- CDC's pre-EUA submission does not include translated versions of fact sheets. Nonetheless, it is possible that any EUA that might be issued by FDA could include conditions relating to distribution of translated fact sheets, or other materials under certain circumstances. If FDA issues an EUA with such conditions, then such translated materials could be distributed along with anthrax countermeasures as described in the EUA. CDC is having proposed doxycycline recipient fact sheets, and proposed ciprofloxacin recipient fact sheets translated into Spanish.

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*HOME PREP INSTRUCTIONS: Must provide home prep instructions at the POD Dispensing/screening procedures*

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- CDC proposed in its pre-EUA submission that doxycycline tablet crushing instructions provided to recipients be the FDA-supplied version, as found at [http://www.fda.gov/cder/drug/infopage/penG\\_doxy/home\\_prep.htm](http://www.fda.gov/cder/drug/infopage/penG_doxy/home_prep.htm). These instructions cannot legally accompany the drugs unless they are authorized under any EUA that might be issued. CDC's pre-EUA submission does not include translated versions doxycycline home preparation instructions. Nonetheless, it is possible that any EUA that might be issued by FDA could include conditions relating to distribution of translated doxycycline home preparation instructions. If FDA issues an EUA with such conditions, then such translated materials could be distributed along with anthrax countermeasures as described in the EUA. CDC is having proposed doxycycline crushing instructions translated into Spanish.
- FDA Doxycycline Pill Crushing Instructions  
<http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM131001.pdf>
- FDA Doxycycline Pill Crushing Instructions (Spanish Version)  
<http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM131008.pdf>
- Ciprofloxacin home preparations instructions are not provided in CDC's pre-EUA submission due to the unpalatable nature of this drug when dissolved and mixed with food.

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*PACKAGE INSERT: Must provide access to the package insert for each medication dispensed at the POD*

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- This may be defined as one hard copy per location, or internet access etc

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*WRITTEN MATERIALS: Must provide written or graphic materials consistent with and not exceeding EUA materials*

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- This includes information provided on posters etc
- Must follow established procedures for authorized changes to ANY written information

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*PACKAGE LABELING: Must follow (Product) labeling requirements*

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- SNS supplied unit of use bottles do not have all the required information on the label (such as patient name, prescriber, etc). CDC's pre-EUA submission proposes that not all of the information required under section 503(b)(2) of the Act would appear on the label of the distributed doxycycline and ciprofloxacin. CDC also proposes that the required Medication Guide label statement for ciprofloxacin not appear on the label. SNS doxycycline and ciprofloxacin will be dispensed with pre-printed labels on the bottles. CDC is not proposing that additional information be added to labels of unit of use bottles of tablets. Project Area planners should plan to dispense ciprofloxacin and doxycycline with labels authorized under any EUA that might be issued.
- CDC is proposing that additional information would need to be added to the label of oral suspensions when dispensing product directly to recipients. Patient's name and dose (in ml) be added to dispensed bottles of oral suspension.

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*DATA COLLECTION: Must collect data and conduct record keeping*

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- Collect, record, and analyze information

- EUA requires that records are kept and made available to FDA upon request. Per other contracts, it also requires that records be kept and submitted as outlined by CDC and State
- Must conduct record keeping and monitoring of adverse events

## VII. Training Opportunities

- 1) **CDC Emergency Use Authorization (EUA) Online Course** <http://emergency.cdc.gov/training/eua/index.html>
- 2) **IND and EUA Overview Video** <https://www.orau.gov/snsnet/resources/videos/IND-EUA-Second-Wed-Video.htm>  
Username: Stockpile Password: Str\*teg!c

## VIII. Resources

- 1) **CDC Key Message Point for New EUAs** [https://www.orau.gov/snsnet/resources/guidance/FinalCDCMessagingPoints01152009\\_ac.pdf](https://www.orau.gov/snsnet/resources/guidance/FinalCDCMessagingPoints01152009_ac.pdf)  
Username: Stockpile Password: Str\*teg!c
- 2) **FDA Current & expired/terminated EUAs** <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>
- 3) **FDA EUA Guidance** <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm>
- 4) **FDA EUA Questions & Answers** <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm153297.htm>
- 5) **FDA Medical Countermeasures Initiative (MCMi)** [www.fda.gov/medicalcountermeasures](http://www.fda.gov/medicalcountermeasures)