

# How FDA Accelerates Medical Countermeasure Development and Availability

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May 2, 2006



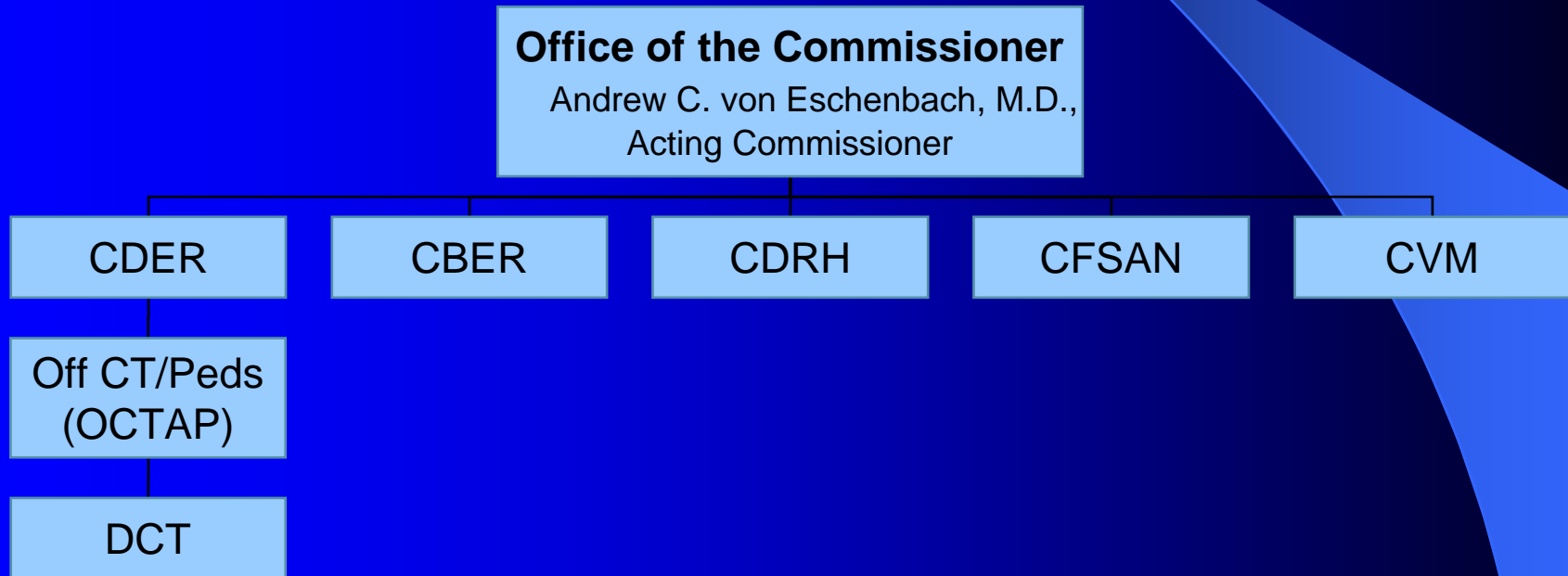
# Overview

- FDA and Drug Development
- Regulatory mechanisms available to facilitate approval of Countermeasures
- Mechanisms to make drugs available during a public health emergency

# FDA Mission

- Protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

# FDA Organization



# Emergency Preparedness is a Priority for FDA

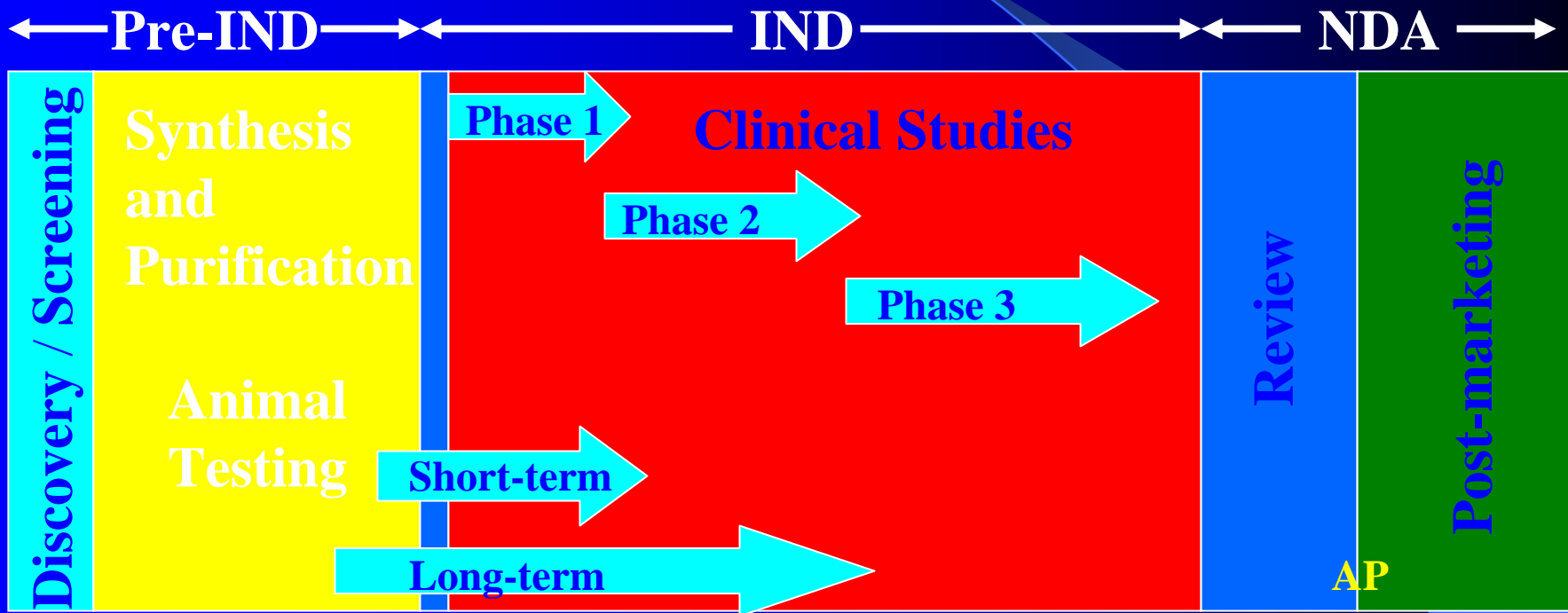
## Response to an Act of Terrorism

- Safety of Food Supply
- Security of Regulated Products
- **Medical Countermeasures**

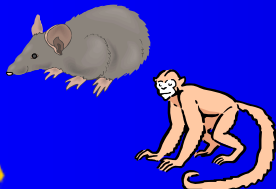
## Response to other Public Health Emergency

- Natural disasters
- Emerging threats

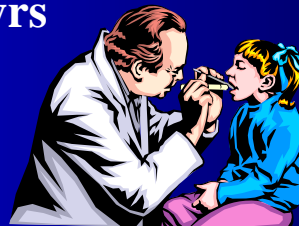
# Drug Development



Avg: 5 - 7 yrs



Avg: 6 - 7 yrs



Avg: 1 yr - Standard  
Avg: 6 mo - Priority

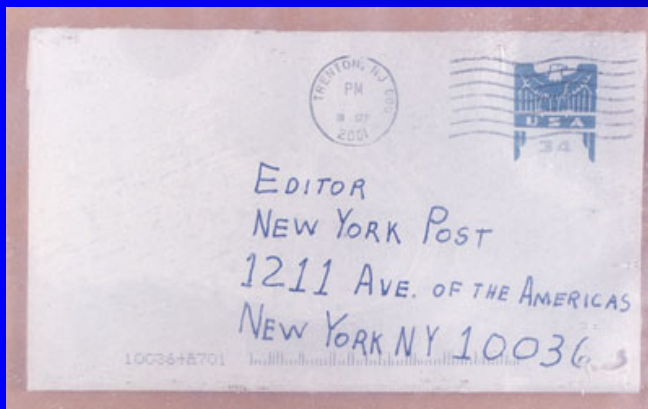
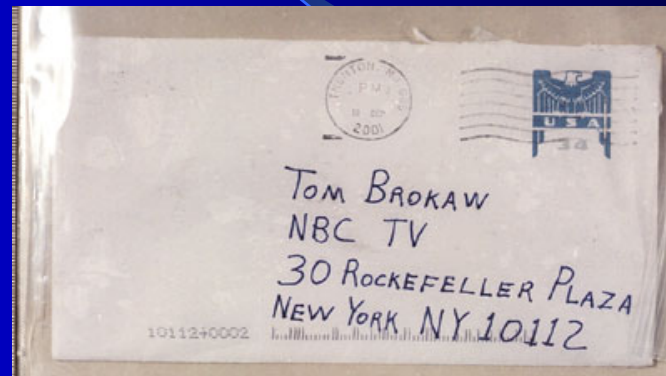
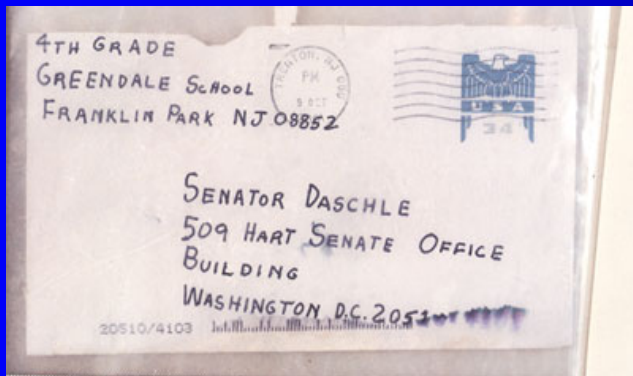


# FDA Approval Requirements

- Safety\*
- Efficacy\*
- Product quality (manufacturing)

\***Substantial evidence** obtained from adequate and well-controlled clinical trials for the intended population

# Drug Development Post-October 2001



# Drug Development Post-October 2001 Continued

- Critical need for medical countermeasures
  - Nuclear/radiological
  - Chemical
  - Biological
- Importance of approved products with approved counterterrorism indications
  - Advantages
    - Strategic
    - Public confidence

# “Practice of Medicine” Exception

- IND regulations do not apply “to the use in the practice of medicine for an unlabeled indication” of an FDA-approved drug product (21 CFR 312.2(d))
- **Implication:** Drugs administered as part of a doctor-patient relationship are not subject to IND regulatory requirements when prescribed for off-label uses
- Not applicable to strategic stockpiles

# FDA and Emergency Response

- Regulations will not impede response to a public health emergency
- Close collaboration with DoD, NIH, CDC , and DHS and other governmental departments and agencies



**In the face of a public health emergency, Americans must have confidence that the medical countermeasures administered to them are safe and effective**

# Mechanism to accelerate Counter-Measure Development

- FDA-sponsor collaboration early in drug development (**Pre-IND**)
- “**Fast Track**” designation during IND
- “**Accelerated Approval**” (**Subpart H**)
- “**Animal Rule**” (**Subpart I**)
- FDA Findings of Safety & Efficacy

# “Fast Track” Designation

- Requested by drug/biologic IND developer
- Serious or life-threatening conditions and/or unmet medical needs
- Allows for a “rolling review” of an application as each “reviewable unit” is submitted

# Accelerated Approval

- Serious or life-threatening conditions
- Therapeutic advantage over existing products
- Surrogates of clinical efficacy used
- Post-marketing studies required
- Final Rule: 11 Jan. 1993

# “Animal Rule”

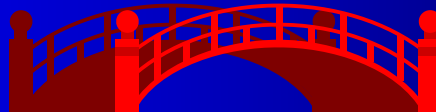
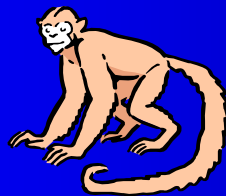
- “Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible”
- Final Rule: 31 May 2002

# “Animal Rule” Requirements

- (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;
  - Explain interspecies differences where they exist

# “Animal Rule” Requirements contd.

- (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 pharmacodynamics of the product or other relevant data or information, in animals and humans, allows **selection of an effective dose in humans**.



# “Animal Rule” Requirements contd.

- (5) All studies subject to this rule must be conducted in accordance with pre-existing requirements under the **good laboratory practices (GLP)** regulations and the **Animal Welfare Act...**
  - GLP allows someone to reconstruct the experiment from start to finish
  - GLP is a quality management system.
- (6) **Traditional safety assessments**
  - Animal toxicology
  - Human

# “Animal Rule”: Limitations on Approval

- Post-marketing studies required
- Approval with restrictions to ensure safe use
  - Where necessary
- Information must be provided to patients
- Restrictions on advertising (pre-approval)
- Product is subject to withdrawal of approval
  - Unsafe or no clinical benefit under conditions of use
  - Safe use cannot be ensured by restricted distribution

# FDA Finding of S&E

- FDA reviews all available data (pre-clinical & clinical) on a drug product and makes a determination of safety and efficacy
- FDA requests submission of manufacturing NDA
- FDA's findings published in the *Federal Register*

# FDA Finding of S&E cont'd

- FR notice may also reference draft labeling proposed by FDA
- Examples:
  - Doxycycline & PCN G - anthrax post-exposure prophylaxis (PEP) (Nov. 2001)
  - Prussian Blue (Jan. 2003)
  - Ca & Zn-DTPA (Sept. 2003)



# How Can FDA Assist In Making MCM or other Products Available During a Public Health Emergency?

# Emergency Access to Medical Countermeasures

- Investigational Countermeasures
  - Emergency IND
  - “Contingency IND”
  - “Streamlined IND”
  - Emergency Use Authorization (EUA)

# Emergency Use Authorization (EUA)

- **Rationale:** Minimize regulatory burden during public health response to a terrorist event
  - IND requirements waived
- **Authority**
  - National Defense Authorization Act (NDAA)
    - Signed into law 11/24/03

# Why EUA?

- Lessons learned from the 2001 anthrax attacks and large-scale smallpox vaccination operational planning
- Conclusion:
  - IND regulations not practicable during a rapidly progressive public health emergency
  - IND process may limit public health's ability to respond and contain the disease/illness

# Criteria for Issuing EUA

- An “emergency” has been declared (or potential)
- Chemical/biological/radiological/nuclear (CBRN) agent is responsible for causing serious, life-threatening disease or conditions
- It is **REASONABLE** to believe that the product **MAY BE** effective in the diagnosis, treatment, or prevention of disease caused by the CBRN agent
- Known benefits outweigh the known risks
- No adequate, approved and available alternative
- Consultation with Directors of CDC and NIH

# EUA Limitations

- EUA information must be provided to patients and healthcare providers
- Responsibility to monitor safety
  - Unapproved product – YES
  - Unapproved use of approved product – “Where practical”
- EUA declaration limited to 1 year (renewable)
  - Subject to early withdrawal

# MEDICAL COUNTERMEASURES(MCM)

EXAMPLES: pre-9/11

1973: AtroPen Atropine Autoinjector - Nerve agent

1979: KI 130mg tablets – Iodine radioisotopes (KI blocks uptake and thereby prevents thyroid cancer)

1983: Pralidoxime Autoinjector - Nerve agent

1990: Diazepam Autoinjector - Nerve agent convulsions

1992: Sodium Thiosulfate Injection - Cyanide

2000: SERPACWA - Skin Exposure Reduction Paste Against Chemical Warfare Agents

2000: Cipro - Inhalational anthrax

# MCM Approvals (2001 to date)

## ● Biological

- Doxycycline and Procaine PCN G for Anthrax PEP
- Levaquin (levofloxacin) for Anthrax PEP

# MCM Approvals (contd.)

## ● Chemical

- Pyridostigmine bromide
- Pediatric atropine autoinjectors

## ● Radiation

- Prussian blue (Radiogardase)
- Calcium & Zn DTPA

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- Lowell Lima, Extramural Programs Chief
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