Critical FDA Pathways to Drug Development

Joanne Holmes, MBA
Office of Counter-Terrorism and Emergency Coordination, CDER, FDA

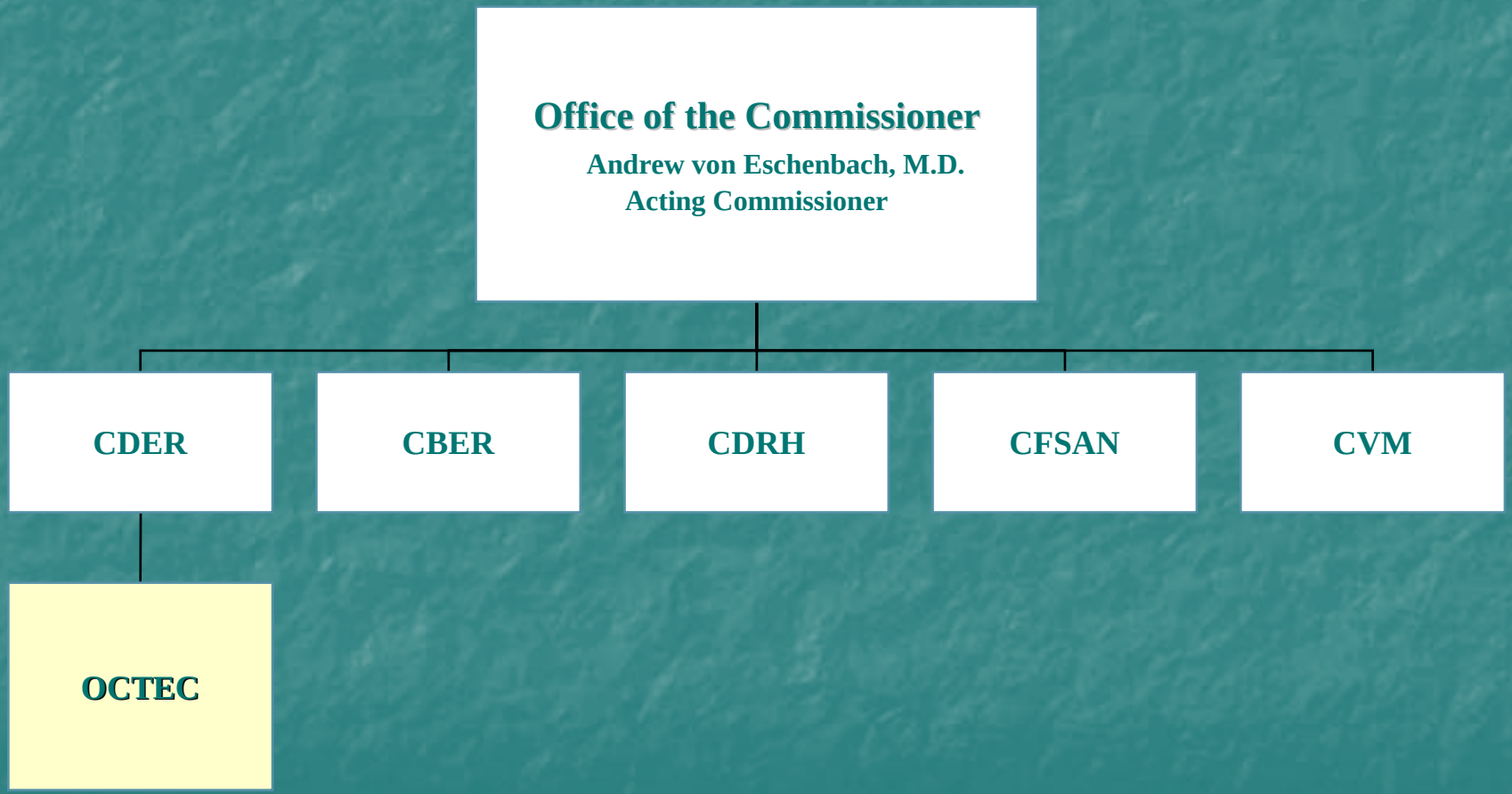
NIAID/CMCR Workshop on the FDA Pre-Market Regulatory Process:
Applications to Radiation Countermeasures After a Large-Scale, Radiological Incident

June 9, 2006

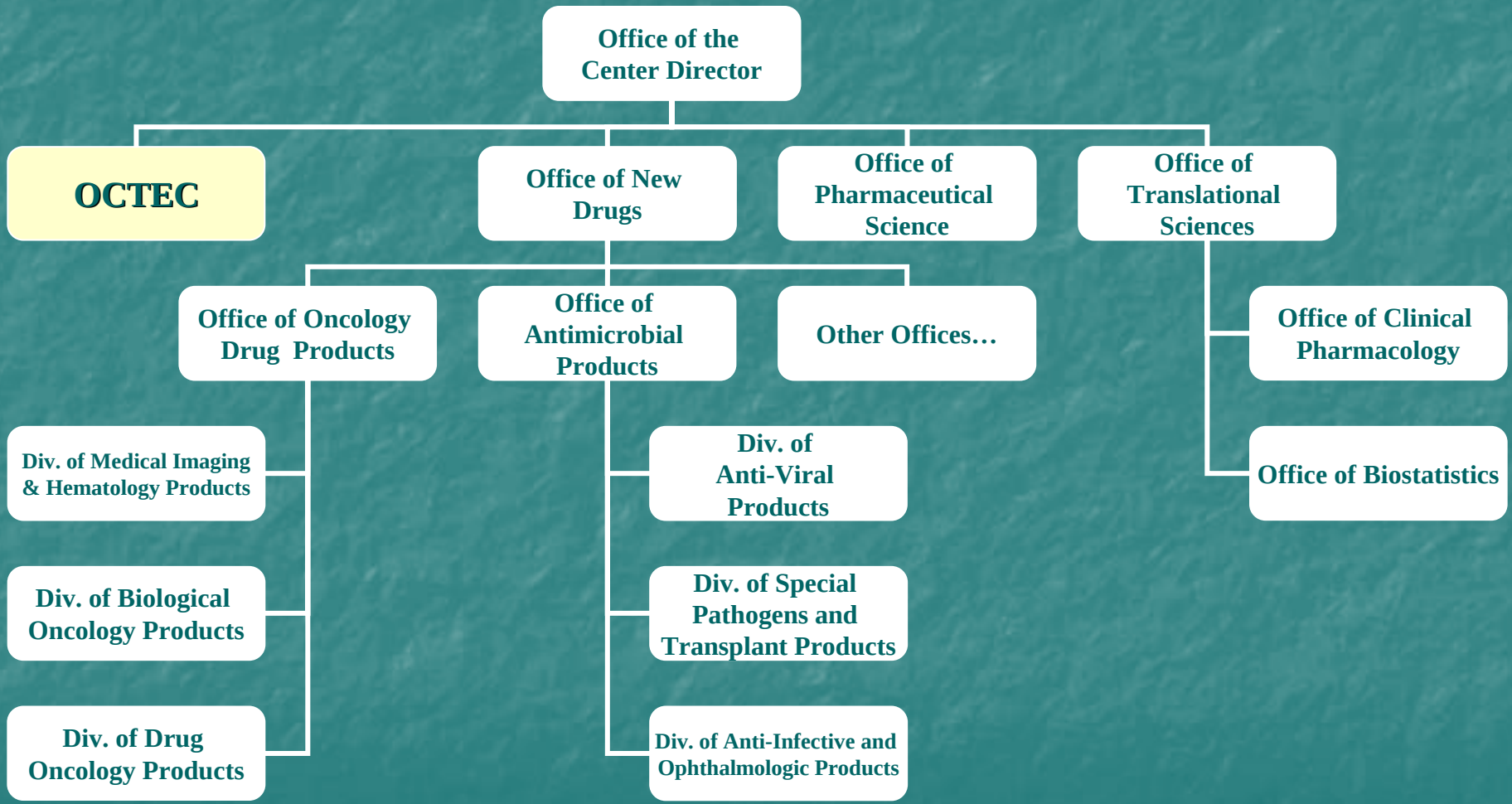
Outline

- FDA/CDER Organization & Mission
- FDA/OCTEC Mission & Role
- FDA Regulated Products
- Requirements for Approval
- Regulatory Pathways
- Access to Unapproved Products

FDA Organization



CDER Organization



Office of Counterterrorism and Emergency Coordination
- Mission -

1. **To facilitate the development and availability of safe and effective medical countermeasures for chemical, biological, radiological, and nuclear threats.**
2. To coordinate emergency operations and responses for CDER pertaining to drugs and biological therapeutics
3. Maintain and exercise CDER's Continuity of Operations Plans (COOP)
4. Coordinate Center activities related to emergency situations involving CDER-regulated products or facilities

Facilitate MCM Development

- CDER POC for early developers of new MCMs
- Pre-, Pre-IND meeting
  - Early advice
  - Assist in identifying potential sources of federal funding
  - General assistance in gauging extent of USG interest in product (e.g., RFI, RFA, RFP)
  - Help identify appropriate OND review division -- when time is right
  - Provide advice about content and organization of meeting package, including questions, to improve efficiency and yield from meetings
- Continue to follow the product's development and attend all meetings between agency and sponsor

Regulated Medical Products

- Drugs are
  - "approved" under Food, Drug & Cosmetic Act (FDCA)
- Diagnostics and Devices are
  - "cleared" under FDCA
- Biologics are
  - "licensed" under Public Health Services Act

Therapeutic biologics are regulated in CDER

Regulatory Status of CT Drugs

- Unapproved (investigational)
- Approved with CT indication
- Approved without CT indication
  - Off-label Use
    - “Practice of Medicine” (legally protected)
    - Interstate Commerce (investigational)

Drug & Biologic Approval Requirements

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

*__Substantial evidence__ obtained from adequate and well-controlled clinical trials for the intended population (i.e., military vs. civilian, including pediatrics, pregnancy, co-morbid conditions, etc.)

What are “Controlled Trials”

1. The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.
2. Types of Control

   (i) Placebo concurrent control

   (ii) Dose-comparison concurrent control

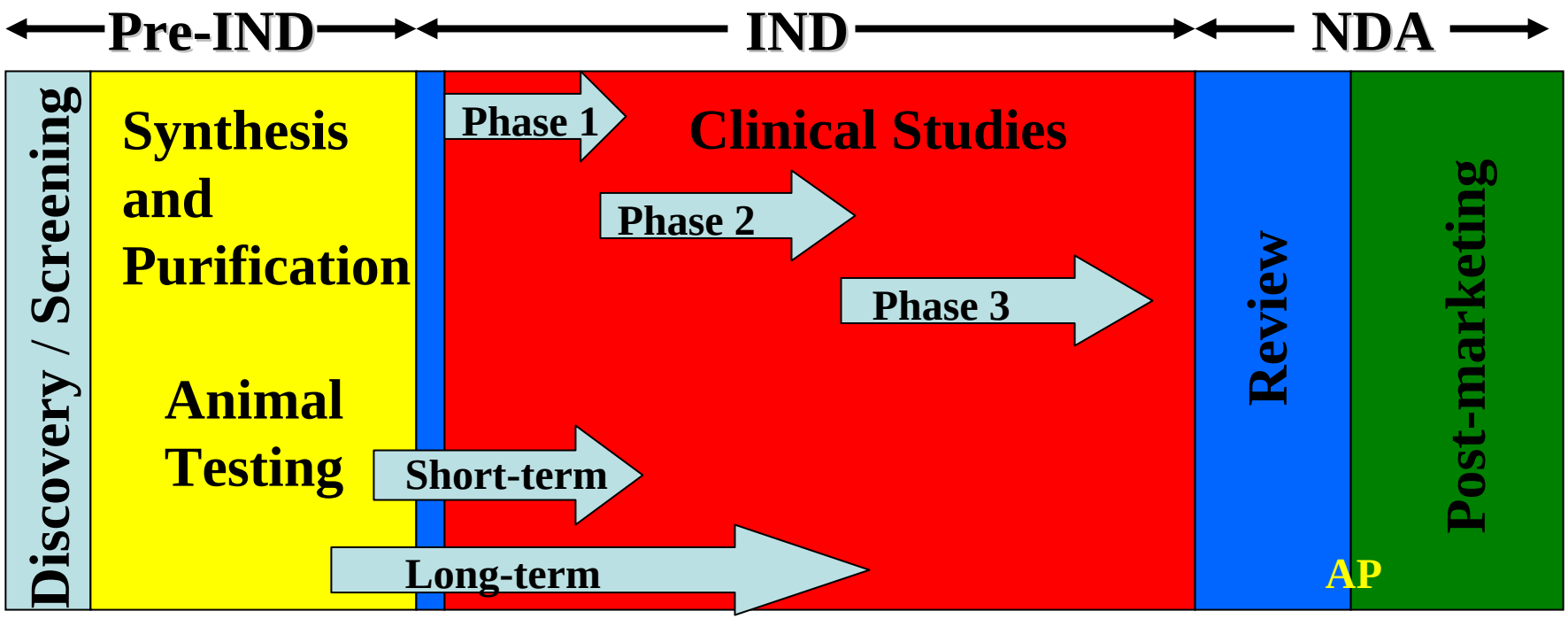
   (iii) No treatment concurrent control

   (iv) Active treatment concurrent control

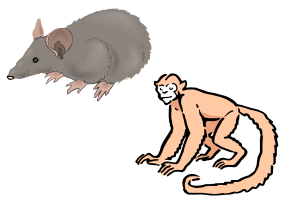
   (v) Historical control

3. The method of selection of subjects provides adequate assurance that they have the disease or condition being studied.
4. The method of assigning patients to treatment and control group minimizes bias and is intended to assure comparability of the groups
5. Adequate measures are taken to minimize bias
6. The methods of assessment of subjects' response are well-defined and reliable.
7. There is an analysis of the results of the study adequate to assess the effects of the drug.

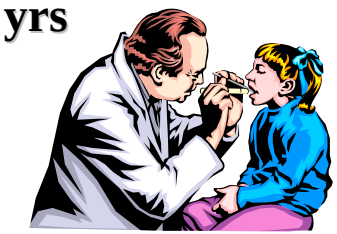
Traditional Drug Development



Avg: 5 - 7 yrs



Avg: 6 - 7 yrs



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

MCM Development Challenges

- Limited availability or access to:
  - Qualified laboratories (GLP)
  - Capability to simulate the condition
  - Choice of animal model(s)
  - Limited animal resources
    - e.g., non-human primates (where necessary)
- Industry: Is there a predictable market?
- Industry: Is there legal protection?

Regulatory Pathways

- Meeting with FDA
- preIND/IND
- Fast Track Designation
- Special Protocol Assessment (SPA)
- Subpart H (Accelerated Approval)
- Subpart I (The “Animal Efficacy Rule”)
- Finding of Safety and Efficacy
- Access to Unapproved Products
  - IND options
  - EUA

Opportunities to Meet with FDA

- **Type A**: Immediately necessary for an otherwise stalled development drug program (e.g., critical path, clinical hold, SPA)
- **Type B**: Pre-IND & certain end of Ph 1, EoPh 2/prePh 3, preNDA/BLA
- **Type C**: Other than Types A or B
- Guidance
  - www.fda.gov/cder/guidance/2125fnl.pdf

Pre IND meeting

- Early dialogue
- Efficiency
  - Multidisciplinary review
  - Identifies areas of focus to plan for first time use in humans
- Resource for developer

IND: Investigational New Drug

21 CFR 312

- An exception to allow an unapproved new drug or biologic to be administered to humans
- Goal: Protect the patient and the public health
- Goal: Provide a pathway for product development and approval, new labeling, or a new indication for an approved product
- Written informed consent is required for enrollment under an IND
- Not crafted with emergency or mass casualty in mind

“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 – interstate commerce

IND Requirements

- **IND Content & Format**: 21 CFR 312.23
  - General investigational plan
  - Investigator's brochure
  - Protocol(s)
  - Chemistry, manufacturing and control information
  - Pharmacology and toxicology information
  - Previous human experience
  - Assurance of IRB review
  - INFORMED CONSENT of participants
- **Focus**: Product development and human subjects protection

Fast Track

- Requested by sponsor (preIND or IND)
- Designation granted by FDA
- Serious or life-threatening conditions and/or unmet medical needs
- “Rolling review” of application as parts submitted
- Not the same as 6 month “Priority” review
  - Fast Track applications likely to receive priority review
  - Priority review does not require Fast Track
- Guidance available (www.fda.gov/cder/guidance/5645fnl.htm)

Special Protocol Assessment

- Protocols eligible for SPA
  - Animal carcinogenicity protocols
  - Final product stability protocols
  - Phase 3 clinical trials - data form the primary basis for an efficacy claim
- Certain protocols evaluated within 45 days to determine if adequate for scientific and regulatory requirements
- Agreements considered binding, unless underlying scientific principles change
- Dependent on understanding developmental context in which protocol is reviewed and questions answered
- Should be discussed in EoPh 2/pre-Phase 3 meeting
- Guidance available for drugs and biologics
  - www.fda.gov/cder/guidance/3764fnl.htm

Subpart H (Accelerated Approval)

- Serious or life-threatening diseases
- Therapeutic advantage over existing treatment
- Efficacy determination uses surrogate markers reasonably thought predictive of clinical benefit
- Post-marketing studies required
- Final Rule effective, January 1993
- 21 CFR 314.500 – 560 (Drugs: Subpart H)
- 21 CFR 601.40 – 46 (Biologics: Subpart E)

Subpart H
FDA may withdraw approval if:

- Post-marketing study fails to verify clinical benefit
- Post-marketing study not conducted with due diligence
- Use demonstrates that post-marketing restrictions are inadequate to insure safe use of the drug
- Post-marketing restrictions not adhered to
- False/misleading promotional materials
- Other evidence shows unsafe or ineffective

Subpart I ("Animal Efficacy Rule")

- "Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible"
- Final rule effective, May 2002
- 21 CFR 314.600 - 650 (Drugs: Subpart I)
- 21 CFR 601.90 - 95 (Biologics: Subpart H)
- Efficacy extrapolation from animal(s)
- Safety from humans
- Consider if Subpart H (Accelerated Approval) not an option

Subpart I: Requirements

1. Pathophysiology of disease and mechanism of action of drug or biologic are reasonably well-understood
2. The effect can be demonstrated in >1 animal species
   - One may be sufficient if species is the most predictive
3. Efficacy endpoints clearly related to human benefit
4. Data are sufficient to identify effective human dose

- Safety assessment and PK studies of drug or biologic itself are conducted in humans
- Post-event safety and efficacy data required

Publication of Finding of Safety and Efficacy

- FDA reviews the available data on a drug product and makes a determination
- FDA's findings are published in the FR
- The FR notice may reference a Guidance on how to submit an NDA for the product
- FR notice may also reference draft labeling
- Examples:
  - Prussian blue for cesium-137 or thallium contamination
  - Ca & Zn-DTPA for plutonium, curium, americium

Access to Unapproved (IND) Drugs or Unapproved Uses of Approved Drugs

- Emergency IND
- Treatment IND
- Emergency Use Authorization (EUA)

Emergency IND (21 CFR 312.36)

- Patients with serious or life threatening illness
- Process: Physician makes request for an individual patient or a small group; all parts of IND not complete at time request is granted
- Informed consent cannot be waived (50.24)
- Limited applicability to mass casualty situation

Treatment IND (21 CFR 312.34)

- Patients with serious or life-threatening illness
- No comparable or satisfactory alternative available
- Drug investigated in controlled clinical trial under IND
- Sponsor is actively pursuing marketing approval

- Product has evidence of safety and efficacy (close to, but slightly lesser standard than “substantial evidence”)
- Other parts of IND required, including informed consent
- Limited applicability in mass casualty

Project BioShield: Emergency Use Authorization (EUA)

- Determination of **domestic emergency** (or significant potential for domestic emergency) by Sec'y of DHS
- Determination of **military emergency** (or significant potential for military emergency) by Sec'y of DoD
- Determination of **public health emergency** that affects (or has significant potential to affect) national security by Sec'y of DHHS

- Secretary of DHHS declares emergency justifying EUA based on one of these determinations (See above.)

EUA contd.

- FDA may authorize the use of certain medical countermeasures during emergencies
  - “Interim Approval” for not longer than one year
  - Requirement for safety and/or efficacy reporting
  - No informed consent requirement
- Draft Guidance: Emergency Use Authorization of Medical Products

Emergency Use Authorization (EUA) Criteria for Issuance

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 diagnosing, treating, or preventing a disease caused by the agent or by a MCM

Emergency Use Authorization (EUA) Criteria for Issuance (contd.)

3. That the known and potential benefits 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; and
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.

OCTEC Program Staff (1)

- Rosemary Roberts, MD, Director
- Brad Leissa, MD, Deputy Director
- Joanne Holmes, MBA, Special Assistant
- Susan McCune, MD
- CAPT Mary Purucker, MD, PhD (on detail)
- CDR Mitchell Mathis, MD
- Lewis Schrager, MD
- CDR Narayan Nair, MD

(301) 796-2210

OCTEC Program Staff (2)

- Larry Cress, MD
- Alla Shapiro, MD
- LCDR Tracy MacGill, PhD (microbiology)
- LCDR Michael Bourg, PharmD
  - Supervisor, Project Management Staff (PMS)
- LTJG Thomas (“TJ”) Christl, MSc (PMS)
- Joan Flaherty, RN (PMS)
- Cheryl Turner, RN, BSN (PMS)
- Su Yang, RN, MSN (PMS)

Useful Web Links

- Drug Applications Site Map
  - www.fda.gov/cder/regulatory/applications/apps-sitemap.htm
- Guidance Documents Page
  - www.fda.gov/cder/guidance/index.htm
- FDA Counterterrorism Page
  - www.fda.gov/oc/opacom/hottopics/bioterrorism.html
- CDER Drug Preparedness and Response to Bioterrorism
  - www.fda.gov/cder/drugprepare/default.htm