Advancements in CBRN Medical Countermeasures

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Outline

• What is BARDA?
• Building the Public Health MCM Enterprise
  — Legislation
  — Governance
  — Requirements
  — Products
• Improving the Public Health MCM Enterprise
  — Medical Countermeasure Review
  — BARDA’s New Roles
• Summary and Forecast
BARDA Mission

Ensuring the availability of countermeasures to address public health emergencies

• Three threat areas: Chem/Bio/Rad/Nuc, Pandemic Influenza, Emerging Infectious Diseases
• Comprehensive portfolio approach to development and acquisition of products
• Unique niche in USG biomedical R&D
  — Bridge the “Valley of Death”
  — Mid- to late-stage product development
  — Staff with experience in product development and manufacturing
  — Work with industry to progress product candidates through the pipeline
BARDA – A Virtual Pharmaceutical Company

5yr R&D Budget Comparison

- Aggregate R&D spend (FY03-08)
- CHIN Project Hold/hold/Advanced Development (FY04-08)
- Pandemic Influenza Advanced Development (FY04-08)

Large Pharma Cohort

Medium & BioPharma Cohort
Phase One – Building the Enterprise

• 2004- 2010
• Legislation
• Governance Structure
• Scoping the Requirements
• Development of Toolkits
• Developing a Pipeline from the Ground Up
• Challenges of Emergency Use Authorization and the FDA Animal Rule
Legislation: The Basics

• Project BioShield Act (JUL 2004)
  — Established Special Reserve Fund
  — Established Emergency Use Authorization (EUA)

• PAHFA (DEC 2006)
  — Established the Office of Assistant Secretary for Preparedness and Response (ASPR)
  — Established BARDA and provided authority to invest in ARD

• PREP Act and Declarations (JAN 2007 to SEP 2009)
  — Limitation of liability related to countermeasures
  — Declarations for specific countermeasures

• Goals: accelerate research, development, purchase, storage and distribution of medical countermeasures
Public Health Emergency Medical Countermeasures Enterprise

National Biodefense Science Board

BARDA
and CDC

FDA

Ex Officio Members:
Scoping the Challenge

Define, Design, Develop, Deliver and Dispense Medical Countermeasures to reduce the adverse health consequences of public health emergencies

A Nation Prepared

Complex array of Threats

Lengthy, risky and expensive product development

Prioritize medical countermeasure programs to effectively address mission goals

Diverse population

Strategies & dependencies for effective use
Radiological and Nuclear agents

Bacteria
*Bacillus anthracis* (anthrax)
*Bacillus anthracis* - multi-drug resistant (MDR anthrax)
*Yersinia pestis* (plague)
*Burkholderia mallei* (glanders)
*Burkholderia pseudomallei* (meliodosis)
*Rickettsia prowazekii* (typhus)
*Franciscella tularensis* (tularemia)
Botulinum toxins (botulism)

Viruses
Variola virus (smallpox)
Hemorrhagic Fever Viruses - Ebola, Marburg, Junin

Volatile nerve agents [determination in progress]
Established through scientific evaluations by scientists, physicians, and public health experts from across the Enterprise

<table>
<thead>
<tr>
<th>The Threat</th>
<th>Target Population</th>
<th>Product Specifications</th>
<th>Deployment and Utilization (CONOPs)</th>
<th>Estimated Requirements</th>
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</thead>
<tbody>
<tr>
<td>✓ Population Exposure Assessment (PEA)</td>
<td>✓ Military</td>
<td>✓ Composition</td>
<td>✓ Deployment logistics</td>
<td>✓ Near-term</td>
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<tr>
<td>✓ Material Threat Determination (MTD)</td>
<td>✓ Civilian</td>
<td>✓ Formulation</td>
<td>✓ Utilization policy</td>
<td>✓ Long-term: replenishment of expired product vs. next generation vs. fill/finish from bulk</td>
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<tr>
<td>Scientific/Medical Characteristics of Threat Agent and Resultant Disease</td>
<td>Available and Next-Generation Countermeasures</td>
<td>✓ Doses per course; are booster doses necessary?</td>
<td>✓ Pre-event</td>
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<tr>
<td>✓ Available medical countermeasures</td>
<td>Formulation and Packaging</td>
<td>✓ Storage requirements/ Stability – shelf-life</td>
<td>✓ Day of event</td>
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<tr>
<td>– Prevention</td>
<td>Desired product specifications for a future generation candidate</td>
<td>✓ Desired product specifications for a future generation candidate</td>
<td>✓ Post-event</td>
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<td>– Treatment</td>
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<td>✓ Available non-medical countermeasures (PPE, etc.)</td>
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<td>✓ Next-generation ideal medical countermeasures</td>
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<td>Medical Consequence Modeling</td>
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Product Specifications

- Composition
- Formulation
- Doses per course; are booster doses necessary?
- Formulation and Packaging
- Storage requirements/ Stability – shelf-life
- Desired product specifications for a future generation candidate
Integrated National Biodefense
CBRN MCM Portfolio
Requirements – Unique and Convergent

DoD-Unique
- Brucellosis Vx
- VEE/EEE/WEE Vx & Rx
- Plague Vx
- Botulism Vx
- SEB Vx & Rx
- Tularemia Vx
- Ricin Vx & Rx
- (other, unfunded)

Common
- Anthrax Vx & Rx
- Smallpox Vx & Rx
- Ebola / Marburg Vx & Rx
- Tularemia Rx
- Botulism Rx
- Radiation Rx
- Nerve agent Vx & Rx

HHS-Unique
- Smallpox Vx for special populations
- Burkholderia sp. Rx
- Junin Rx
- Plague Rx

DoD focus is on protecting forces prior to exposure. HHS focus is on response to threats to general civilian population after exposure

V_x = Prophylaxis  R_x = Therapeutic
CBRN Toolkits
For Emergency Preparedness

- **Anthrax**
  - Antibiotics
  - Vaccines
  - Antitoxins

- **Smallpox**
  - Vaccines
  - Therapeutics

- **Botulism**
  - Heptavalent Antitoxin

- **Bacterial Threats**
  - Antibiotics

- **Rad/Nuc**
  - Ca- & Zn-DTPA
  - Prussian Blue
  - Potassium Iodide
  - ARS Therapeutics
  - Burn/Blast Supplies

- **Chem**
  - CHEMPACKs

- **E. D.**
  - Vaccines
  - Diagnostics
  - Antivirals
HHS CBRN Countermeasure Development Funding

**PHASES**
- Discovery
- Preclinical Development
- Phase I
- Phase II
- Phase III
- Licensure
- Production & Delivery

**NIH ($12.7B)**

**BARDA ($786M)**

**Project BioShield ($5.6B)**

**PRODUCT PIPELINE**
- **PROBABILITY OF SUCCESS TO LICENSURE**
  - 1-3%
  - 5-17%
  - 10-25%
  - 18-35%
  - 45-70%
  - 90%

**TIME**
- 3-7 yr
- 0.5-2 yr
- 1-2 yr
- 2-3.5 yr
- 2.5-4 yr
- 1-2 yrs

**PIPELINE PHASE COST**
- $100M - $130M
- $60-70M
- $70M-100M
- $130M-160M
- $190M-220M
- $18M-20M
Development is Expensive, Lengthy and High Risk

• Industry benchmarks for typical drug
  — 10-15 yrs from bench to pharmacy
  — $700M to $1B investment
  — Very low probability of success

• BARDA’s mission is to develop MCMs for each of the current material threat determinations
  — Phase 2 to licensure 6-8 yrs
  — ~$350M per MCM
  — 13 threats X $350M X one MCM = $4.6 B
  — This does not include procurement and stockpiling
• **Important points**
  - Animal rule concerns the approval of new drug or biological products when human efficacy studies are neither ethical nor feasible
  - Testing under the Animal Rule is a surrogate for human efficacy/clinical studies
BARDA CBRN Business Model

• “Truth Seeking”
  – Emphasis on Proof of Concept
  – Early R&D
  – Integration of platforms, CROs, CMOs
  – Relies on tech-transfers, data and model sharing
  – Rapid Go/No Go

• “Success-Seeking”
  – Emphasis on licensure and stockpiling
  – Scale-up, validation of manufacturing
  – Phase II/III, pivotal animal studies
  – Life cycle and sustainment important
CBRN Late-Stage Programs

- **Smallpox Vaccine**
  - 1\textsuperscript{st} generation
  - 2\textsuperscript{nd} gen. attenuated strain

- **Anthrax Antitoxins**
  - Anti-PA monoclonal antibody
  - Anthrax immunoglobulin

- **Anthrax Vaccine (1\textsuperscript{st} Generation)**
  - Anthrax vaccine for post-exposure prophylaxis

- **Botulism Antitoxin**
  - Heptavalent product
Early Development Pipeline

- **Anthrax**
  - Vaccines – novel adjuvants and formulations
  - Antitoxins – enhanced affinity

- **Smallpox**
  - Antivirals
  - Vaccine enhancement

- **Hemorrhagic fever viruses**
  - siRNA-based antivirals
  - Post-exposure prophylactic vaccines

- **Broad-spectrum antimicrobials**
  - Inhalational delivery systems
  - Dual-use antibiotics

- **Radiation/Nuclear**
  - Therapeutics for acute radiation syndrome and burns
  - Decorporation agents

- **Biodosimetry**
  - Devices and assays
Phase Two – Improving the Enterprise

• 2011 and Beyond
• Lessons Learned from Influenza Pandemic
• Revision of the Mission
• MCM Enterprise Reviews and 4 New Initiatives
• Antimicrobial Broad Spectrum Approach
• Animal Models Consortia of Developers
The MCM Enterprise Vision

“Our Nation must have the nimble, flexible capacity to produce MCMs rapidly in the face of any attack or threat, known or unknown, including a novel, previously unrecognized naturally occurring emerging infectious disease”

If a product fails, it should only be the result of failure of the product to achieve the desired safety or efficacy thresholds, and not as a function of our inability to provide the proper support from a technical, business and regulatory perspective
2010 MCM Enterprise Review

- Enhancing regulatory innovation, science, and capacity
- Provision of core development and manufacturing services to innovators and MCM developers
- Expansion of flexible, surgeable manufacturing capacity
- Novel ways to work through public–private partnerships and support for pre-competitive collaborations
- Financial incentives for MCM development
- Addressing roadblocks from concept to advanced development
- Improved management and administration
• **Goal 1:** An advanced development pipeline replete with medical countermeasures….. emphasizing innovation, flexibility, multipurpose, broad spectrum application, and long-term sustainability

• **Goal 2:** Provide core services to MCM innovators

• **Goal 3:** Agile, robust and sustainable U.S. manufacturing infrastructure

• **Goal 4:** Responsive and nimble programs and capabilities to address novel and emerging threats

• **Goal 5:** Capabilities to develop, manufacture and facilitate distribution of MCMs during emergencies
How Can We Sustain This Enterprise?

• **Product Improvements**
  — Enhance shelf life
  — Potency, immunogenicity

• **Stockpiling of manufacturing intermediates**
  — Frozen bulk products
  — Requires rapid fill/finish capabilities

• **Develop multi-use products – antimicrobials**

• **Repurpose existing FDA approved products**

• **Integrate stockpiling with existing drug inventories**
What CBRN Products Do We Still Need?

• Broad-spectrum antimicrobials
  — Co-funding biodefense with other indications

• Radiation countermeasures
  — Acute radiation countermeasures
  — Oral decorporation agents
  — Biodosimetry/bioassays
  — Skin/lung countermeasures

• Anthrax vaccines
  — Faster-acting, stable, cheap

• Diagnostics – all agents

• Volatile nerve agent countermeasures
  — Enterprise ChemPak improvements
  — Single antidote
BSA Program: Public Health Need

• Infections are the #3 cause of death in the US
• Infections are the #2 cause of death in the world
  — 14.9 million in 2004 (29% of all deaths)
• Hospital acquired infections: 2 million per year in US
  — 90,000 deaths
• Antibiotic resistance cost the health care system more than $8 billion in 2006
• Resistance to most classes of antibiotics has increased to an extent that infections in some patients are untreatable by current antibiotics
• Large pharma has largely abandoned R&D investment in antimicrobials

WHO World Health Report, CDC, IDSA “Bad Bugs, No Drugs, GAO report, Clin Infect Disease
Public-Private Partnerships

- New approach for development of multi-use drugs
- Biodefense and antibiotic resistance indications sought
- Supported by Pandemic and All Hazards Preparedness Act and the Secretary’s MCM Enterprise Review
- August 30, 2009 – Achaogen Inc. contract valued up to $64M for plague/tularemia/ventilator-induced pneumonia/catheter-induced UTI
Plazomicin

- BARDA contract (Aug. 2010) to Achaogen to develop a ACHN-490 (Plazomicin)

- Biodefense indications: plague and tularemia

- Hospital-acquired infection indications: complicated Urinary Tract Infection (UTI), Hospital/Ventilator Acquired Pneumonia (HAP/VAP)

- Overcomes resistance mechanisms that defeat commonly used aminoglycosides
GSK052

• BARDA contract ($94M) for the development of a novel class of antibiotic

• Biodefense indications: anthrax, plague, and tularemia

• Hospital-acquired infections indications: complicated intra-abdominal infection, HAP/VAP, complicated UTI

• Drug candidate is first novel antimicrobial to treat hospital acquired Gram (-) in 40 years

• $50M dedicated to Phase III cIAI study (cost sharing)
Summary and Forecast

• **MCM Advanced Development & Manufacturing**
  – Supporting Product Development
  – Manufacturing and Animal Models

• **MCM Stockpiles**
  – Sustainment
  – Versatility
  – Funding

• **Key Enhancements to the Enterprise**
  – Importance of FDA Initiative
  – USG manufacturing
Interfacing with BARDA

• [www.hhs.gov/aspr/barda](http://www.hhs.gov/aspr/barda)
  — Program description, information, news, announcements

• [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)
  — Portal to BARDA
  — Register, request a meeting
  — Tech Watch

• [www.fedbizopps.gov](http://www.fedbizopps.gov)
  — Official announcements and detailed information about all government contract solicitations
  — [gerald.kovacs@hhs.gov](mailto:gerald.kovacs@hhs.gov)