Processes and Products for Preparation and Response

The Public Health Emergency Medical Countermeasures Enterprise

George W. Korch, Ph.D.
Senior Science Advisor
Assistant Secretary Preparedness and Response

July, 2015
• Federal coordinating body, led by HHS, that protects the U.S. civilian population from national health security threats through the use of medical countermeasures (MCMs)
  — Chemical, biological, radiological, and nuclear agents
  — Emerging infectious diseases (including influenza)
  — Member agencies include:
    o HHS: ASPR (including BARDA), CDC, FDA, and NIH
    o DoD, DHS, VA, and USDA

• Develops, produces and makes available medical countermeasures that limit adverse health impacts
  — Medical countermeasures are medicines, devices, or other medical interventions that can lessen the harmful effects of these threats
Events are unpredictable, and each presents a chance to improve for the next
Globalization and the Reality of Health Security

The Future?
Growth in International Air Traffic Carrying Capacity

“Recognizing that the health of the world’s population has never been more interdependent, we are improving our public health and medical capabilities […] include [ing] our ability to work with international partners to mitigate and contain disease when necessary.”

- National Security Strategy, 2010
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Medium range: Aerosol Release</th>
<th>Low range: 2001 Anthrax Attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number that would need</td>
<td>1.9-3.4 M</td>
<td>30,000</td>
</tr>
<tr>
<td>antibiotic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of illnesses</td>
<td>~450,000</td>
<td>22</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>~380,000</td>
<td>5</td>
</tr>
<tr>
<td>Decontamination</td>
<td>City wide</td>
<td>6 Buildings</td>
</tr>
<tr>
<td>Direct Economic Cost</td>
<td>&gt;$1.8 T</td>
<td>&gt;$1 B</td>
</tr>
<tr>
<td>Decontamination</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Biological Defense Must Address a Range of Scenarios**

**1 gm via letters**

- Biological Defense Must Address a Range of Scenarios
- **Low range: 2001 Anthrax Attacks**
- **Medium range: Aerosol Release**

**Number that received antibiotic treatment**: 30,000

**Number of illnesses**: 22

**Number of deaths**: 5

**Decontamination**: 6 Buildings

**Direct Economic Cost**: >$1 B

**1-2 kg via cropduster**

- Biological Defense Must Address a Range of Scenarios
- **Low range: 2001 Anthrax Attacks**
- **Medium range: Aerosol Release**

**Number that would need antibiotic treatment**: 1.9-3.4 M

**Number of illnesses**: ~450,000

**Number of deaths**: ~380,000

**Decontamination**: City wide

**Projected Economic Cost**: >$1.8 T
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
PHEMCE Lead Roles

Key
- PHEMCE Mission Components
- HHS PHEMCE Agencies
- Non-HHS PHEMCE Agencies
- Non-Federal Stakeholders

Acronyms
- PHEMCE: Public Health Emergency Medical Countermeasure Enterprise
- DHS: Department of Homeland Security
- DoD: Department of Defense
- USDA: U.S. Department of Agriculture
- VA: Department of Veterans’ Affairs
- HHS: Department of Health and Human Services
- ASPR: Assistant Secretary for Preparedness and Response
- BARDA: Biomedical Advanced Research & Development Authority
- CDC: Centers for Disease Control and Prevention
- FDA: Food and Drug Administration
- NIH: National Institutes of Health
Ebola Vaccine & Drug Development is Still Expensive, Lengthy, & Risky

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

PRODUCT PIPELINE:
- NIH ($11.8B)
- BARDA ($540M)
- Project BioShield ($5.6B)

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
- $60M-100M
- $70M-100M
- $130M-160M
- $190M-220M
- $18M-22M

Ebola MCMs 2014

Valley of Death


- 11% success rate
- 10+ years
- $2.6B per drug
No Single Agency has Visibility into the Entire MCM Development Portfolio

- **Basic Research**
  - In Vitro & Animal Models
  - Animal Testing
  - Lab-Scale Production

- **Preclinical Development**
  - Human & Animal Efficacy, Dose, & Safety Testing
  - Formulation
  - Production of Clin. Supplies

- **Clinical/Non-clinical Development**
  - Regulatory Submission
  - Manufacturing Scale-Up

- **Filing & Launch preparation**
  - Full-Scale Production
  - Safety Follow-Up

- **Commercialization & Procurement**
  - Warm base production

- **Readiness & Stockpiling**

**Civilian Programs**

- **NIH**
- **ASPR-BARDA**
- **ASPR-OPEO**
- **CDC**

**Military Programs**

- **DARPA**
- **CBDP**
- **DTRA-JSTO**
- **JPEO-JPM MCS**
- **Individual Services**
High-Priority Threats

- Bacillus anthracis (anthrax)*
- Clostridium botulinum toxin (botulism)*
- Cyanide
- Emerging infectious diseases
  - Pandemic influenza
- Gram negative organisms
  - Francisella tularensis (tularemia)
  - Yersinia pestis (plague)
  - Burkholderia mallei (glanders)
    and B. pseudomallei (meliodosis)
  - Rickettsia prowazekii (typhus)
- Multi-drug resistant Bacillus anthracis (MDR anthrax)

The PHEMCE will continue to address medical countermeasure needs to protect against high priority threats which have been determined by the Secretary of Homeland Security to pose a material threat sufficient to affect national security and/or which have the potential to seriously threaten national health security

- Nerve agents
- Radiological agents
  (e.g., radiological dispersal devices)
- Nuclear devices
- Variola virus (smallpox)*
- Viral Hemorrhagic Fevers
  - Marburg
  - Ebola

* As significant progress accrues for these threats there will be greater attention paid to the next most important agents over time.
The Evolution of the PHEMCE

- Initiated with the advent of Project BioShield and creation of the Biomedical Advanced Research and Development Authority 2005-2006
- Consolidated around creating the 2007 plan for product development
- Re-organized following the 2010 HHS Secretary report on improving medical countermeasure development
- Expanded to incorporate end-to-end visibility and pandemic influenza needs in 2010
- Updated Strategy and Implementation Goals in 2012
  - [http://www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx](http://www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx)
- Recognized in 2013 reauthorization of the Pandemic and All-Hazards Preparedness Act for specific deliverables
Key PHEMCE Documents
PHEMCE Prioritization Framework

• All Actions in PHEMCE are based on Two Core Principles
  – Limit adverse health impact
  – Stewardship of resources that create an enduring capability

• Product decisions will be judged against these criteria:
  • Focused on key threats
  • Potential for multi-functional product
  • Forecasts operational capacity
  • Addresses needs of at-risk population needs
  • Optimizes cost and time for product development / use

• New processes for overall portfolio management are being instituted
PHEMCE Governance Structure

Enterprise Senior Council (ESC)
Policy and Strategy
(Chair: Dr. Lurie)

Enterprise Executive Committee (EEC)
Coordination and Communication
(Co-chairs: Drs. Korch and Kaplowitz)

Project Coordination Teams (PCTs)
Acquisition and Advanced Development

Integrated Program Teams (IPTs)
End-to-End Portfolio Vision

Portfolio Advisory Committee (PAC)
HHS – DOD Portfolio Planning

Requirements Working Groups

January, 2015

Dr. Nicole Lurie, ASPR
Dr. Tony Fauci, NIAID
Dr. Steve Ostroff, FDA
Dr. Tom Frieden, CDC
Dr. Tom Hopkins, DoD
Dr. Kathy Brinsfield, DHS
PHEMCE Integrated Program Teams (IPTs)

- Anthrax
- Botulism
- Broad Spectrum Antimicrobial (BSA)
- Chemical
- Diagnostics
- Pediatric and Obstetric (PedsOB)
- Radiological/Nuclear (Rad/Nuc)
- Smallpox
- Viral Hemorrhagic Fever (VHF)
- Product Monitoring and Assessment

- Flu Risk Management Meeting
- Emerging Diseases WG
Integrated Portfolio for CBRN MCM: Requirements – Unique and Convergent

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

V_x = Prophylaxis  R_x = Therapeutic
Incorporating Capabilities into PHEMCE CBRN Requirements Architecture

Threat Assessment

Needs Analysis

Capabilities Assessment

Response Integration

Acquisition

Research & Development Solution

Off-the-Shelf Solution

What are the threats?

What and how much do we need?

What is the CONOPs framework?
How much can we use?
What should the product look like?

Decision

What are the FINAL CONOPs?

How much do we buy?
Ongoing PHEMCE Activities

- PHEMCE Strategy and Implementation Plan (SIP)
- Strategic National Stockpile Annual Review (SNS AR)
- Portfolio Reviews
- Multi-Year Budgeting
- Portfolio Tracking Tools
- Preparedness Determinants
- Strategic Plans Crosswalks
2014 PHEMCE Strategic Goals

Goal 1
- Identify, create, develop, manufacture and procure critical medical countermeasures

Goal 2
- Establish and communicate clear regulatory pathways to facilitate MCM development and use

Goal 3
- Develop logistics and operational plans for optimized use of medical countermeasures at all levels of response

Goal 4
- Address medical countermeasure gaps for all sectors of the American civilian population
Implementation Plan Synopsis

• Sections
  – Activities to achieve strategic goals and objectives
  – Interagency partnership roles and collaborations
  – Activities identified by specific threats
  – Broad spectrum and Capabilities Actions

• Over seventy major milestones identified

• Every action is assigned to a specific lead agency

• Projected completion times are provided for next 4 years

• Major emphasis on special populations, product development, regulatory science, operational plans and building a sustainable infrastructure
## Advanced Development (AD) and Procurement Priorities

### Medical Countermeasure Category

<table>
<thead>
<tr>
<th>Medical Countermeasure Category</th>
<th>AD Priorities Through FY17¹</th>
<th>Current HHS Holdings²</th>
<th>Procurements Programmed Through FY13³</th>
<th>Additional Procurements Projected Through FY17⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax Antitoxin</td>
<td>X</td>
<td>X</td>
<td>SRF⁵</td>
<td>TBD⁶</td>
</tr>
<tr>
<td>Anthrax Vaccine</td>
<td>X</td>
<td>X</td>
<td>DSNS⁷</td>
<td>DSNS, TBD</td>
</tr>
<tr>
<td>Botulism Antitoxin</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad Spectrum Antimicrobials</td>
<td>X</td>
<td>X⁸</td>
<td>DSNS</td>
<td>DSNS, TBD</td>
</tr>
<tr>
<td>Cyanide Antidote</td>
<td>X</td>
<td>X</td>
<td>DSNS</td>
<td></td>
</tr>
<tr>
<td>Diagnostics – Bioassay</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostics – Biodosimetry</td>
<td>X</td>
<td></td>
<td></td>
<td>TBD</td>
</tr>
<tr>
<td>Diagnostics – Biological Agents</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostics – Pandemic Influenza</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostics – Volatile Nerve Agents</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve Agent Antidote</td>
<td>X</td>
<td>X</td>
<td>DSNS, SRF</td>
<td>DSNS</td>
</tr>
<tr>
<td>Nuclear Agents – Acute Radiation Syndrome (ARS) – Gastrointestinal (GI), Skin, and/or Lung Therapeutics</td>
<td>X</td>
<td></td>
<td></td>
<td>TBD</td>
</tr>
<tr>
<td>Nuclear Agents – ARS – Hematopoietic Therapeutics</td>
<td>X</td>
<td>X</td>
<td>SRF</td>
<td></td>
</tr>
<tr>
<td>Nuclear Agents – Thermal Burn Therapeutics</td>
<td>X</td>
<td>X</td>
<td>DSNS</td>
<td>TBD</td>
</tr>
<tr>
<td>Pandemic Influenza Antivirals</td>
<td>X</td>
<td>X</td>
<td>DSNS</td>
<td>TBD</td>
</tr>
<tr>
<td>Pandemic and Pre-Pandemic Influenza Vaccine</td>
<td>X</td>
<td>X</td>
<td>DSNS</td>
<td>DSNS</td>
</tr>
<tr>
<td>Patient (Chemical) Decontamination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiological Agents – Decorporation/Blocking Agents</td>
<td>X</td>
<td>X</td>
<td>DSNS</td>
<td>DSNS, TBD</td>
</tr>
<tr>
<td>Respiratory Protective Devices</td>
<td>X</td>
<td></td>
<td>DSNS</td>
<td></td>
</tr>
<tr>
<td>Smallpox Antivirals</td>
<td>X</td>
<td>X</td>
<td>SRF</td>
<td></td>
</tr>
<tr>
<td>Smallpox Vaccine</td>
<td>X</td>
<td>X</td>
<td>DSNS, SRF</td>
<td>DSNS, TBD</td>
</tr>
<tr>
<td>Ventilators</td>
<td>X</td>
<td>X</td>
<td>DSNS</td>
<td></td>
</tr>
<tr>
<td>Viral Hemorrhagic Fever Antivirals</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Hemorrhagic Fever Vaccine⁹</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Footnotes:

1. These priorities include new products coming through the advanced development pipeline, as well as enhancements to current products in the SNS.
2. Includes inventory held in both the SNS and alternative stockpiles
3. Contingent upon available resources
4. Assuming appropriations are available to maintain currently stockpiled and programmed levels
5. Solicitations are ongoing to maintain existing preparedness levels and manufacturing capacity established under previous contracts.
6. To Be Determined - Purchase of medical countermeasures under Project BioShield are planned pending appropriations
7. DSNS refers to the Division of Strategic National Stockpile, the CDC division responsible for managing the SNS, whose mission is to deliver critical medical assets to the site of a national emergency.
8. This includes antimicrobials for the following threat agents: anthrax, plague, tularemia, typhus, and secondary infections resulting from radiological and nuclear agents or pandemic influenza.
9. Advanced development of this MCM class is not expected until the long-term, but early stage research is ongoing.
New Products Projected for SNS 2015-2019

“New MCMs emerging from the current BARDA development pipeline that are mature enough for late-stage development and procurement under BioShield and qualify for utilization in an event under Emergency Use Authorization from FYs 2014-2018 include the following products:

- Next generation artificial skin replacement therapy for definitive care treatment of thermal and radiation burns (FY 2015);
- Antimicrobial drug-impregnated mesh dressings for point-of-care treatment of thermal and radiation burns (FYs 2017-2018);
- Multiple broad spectrum antibiotics for treatment of anthrax, plague, tularemia, and other biothreats (FYs 2017-2018);
- Gene expression- and other technology-based biodosimetry devices for quantitative measurement of ionizing radiation exposure in affected persons following a nuclear event (Initial procurement FY 2016 and additional funds will be necessary in FY 2016);
- Chemical antidotes for cyanide poisoning and highly-volatile nerve agents (FYs 2016-2018);
- Multiple therapies using cell-based, recombinant protein, and small molecule technologies for treatment of hematopoietic, skin/lung, and gastrointestinal illnesses associated with ARS (FYs 2016-2018);
- Next-generation anthrax vaccine and adjuvanted enhancement to the current anthrax vaccine (FYs 2016-2018);
- New lyophilized MVA smallpox vaccine for “at-risk” individuals which will provide a significant lifecycle costs savings (FY 2016);
- A second smallpox antiviral drug fulfilling the Public Health Emergency Medical Countermeasures Enterprise requirement for two smallpox antiviral drug products (FY 2015);
- A monoclonal anthrax antitoxin that is currently being developed under ARD to improve the lifecycle management costs for stockpiling this type of MCM (FY 2015); and,
- Therapeutics and vaccines for Ebola currently funded under ARD, which will be evaluated for efficacy in the United States and West Africa (FY 2016).”
• Develop PHEMCE common business processes and tools based on harmonized metrics to use for PHEMCE portfolio tracking, coordination and management of the Integrated National MCM Portfolio
  – Current PHEMCE Agencies and Partners utilize their own sets of processes and tools to varying degrees for project, program and portfolio management of MCM development

• Harmonized set of Quantitative Technological Readiness Levels (Q-TRLs) for MCMs
  – QTRLs represent development milestones and activities from discovery through post-approval

• Microsoft Excel-based business tool to collect high-level project information including scope, schedule, and budget for the purposes of portfolio analyses and reporting
Portfolio Tracking and Coordination Initiative to Provide Key Decision Support Capabilities

.......that currently do not exist within the PHEMCE

Common language for MCM development activities across all Agencies

Early identification of key areas for collaboration across the MCM development space

Rapid access to current “apples to apples” information across the integrated national portfolio

Visibility to reduce duplication of activities between Agencies

Cost estimation and analysis with high degree of accuracy and data confidence
Data and Information Output

Project Level Output

Each contract/project level file will capture relevant information: static, cost, schedule, performance and provide a dashboard for real-time analysis.

- High-level (not project mgmt)
  - Cost
  - Schedule
  - Performance

- Static information
  - Contract data
  - Indication being pursued
  - Requirement being supported
  - Contracting types, SBA Info (small business)
  - Funding Types (Color of money)
  - And Others as required by stakeholders

Portfolio Level Output

A business intelligence analytics and reporting engine will allow for custom dashboards and reports as well as *ad hoc* analytics and reporting.

- Benchmarking
- Risk management
- Resource demand
- Investments by threat
- Pipeline maturity
- Budget allocation
- Budget and resource planning
- Strategic alignment
- Performer analysis
- Agency-specific SBA Reports
This system is enabling real-time web-based data hosting, upload, analytics and reporting. For the first time all PHEMCE data is commonly structured, consolidated and available for analysis down to the individual contract level.
Portfolio Level Budget Analyses

Overall Spending on MCM by Agency
- JSTO/DTRA: 15%
- JPM-TMT: 18%
- JPM-CBMS: 24%
- BARDA: 28%
- NIH: 15%

Overall Spending by Threat Area
- Anthrax: 19%
- VEE/EEE/MEE: 20%
- Botulism: 13%
- Chem: 10%
- Rad-Nuc: 10%
- Smallpox: 17%
- Filovirus: 11%
Preparedness Determinants
The Strategic Need for Preparedness Assessment

• **PHEMCE Preparedness Goal:**
  Ability to properly deliver MCM’s to the correct population at the time of need

• Components have been developed with EEC, ESC, and NPRSB concurrence over the past year.

• We have settled on a methodology that defines common elements across all MCM’s so that progress is measurable and we can assess gaps.

• Overarching goal is to have ability to judge how prepared we are against each threat
Preparedness Goal Determinants

- Research and Development ("develop")
- Manufacturing Capacity ("make")
- Procurement and Stockpiling ("access")
- Response Planning and Guidance ("plan")
- Operational Capacity ("use")
Visualizing Preparedness for an MCM Class

Operational Capacity

Key:
- Preparedness Goal
- Current
- Target

Need

Response Planning and Guidance
Plan?

Current

Target

Procurement and Stockpiling
Access?

R&D
Develop?

Manufacturing Capacity
Make?

ASPR
Assistant Secretary for Preparedness and Response
Biomedical Advanced Research and Development Authority (BARDA)
BARDA Created a Robust & Productive MCM Development Pipeline

- More than 150 MCM product candidates in development since 2004
BARDA MCMs under Project BioShield

Smallpox

Radiation

Anthrax

Chemical

Botulism
BARDA Has Established Robust CBRN MCM Development Pipeline

- **BARDA CBRN MCM development pipeline has supported 89+ candidates since 2004 ($2.5 B)**

- **Biothreats**
  - Anthrax vaccines (7) and antitoxins (7)
  - Smallpox vaccine (3) and antiviral drugs (2)
  - Botulinum antitoxin (1)
  - Other biothreat antimicrobial drugs (7)
  - Viral Hemorrhagic Fever (6)

- **Rad/Nuc threats**
  - Acute Radiation Syndrome drugs (36)
  - Decorporation agents (6)
  - Thermal burn therapies (9)
  - Biodosimetry devices (11)

- **Chem threats** – antidotes & decon (4)
Cell-based Influenza Vaccine

Influenza IV Antiviral Drug

Recombinant-based Influenza Vaccine

Protein Sciences Corp.

H1N1 & H5N1 Vaccine w/ Adjuvant

GlaxoSmithKline

Botulinum Antitoxin

HGS/GSK

Novartis

Cangene

Flu/RSV POC Diagnostic

3M/Focus

Next-Gen Portable Ventilators

Covidien
• Influenza vaccine development
  – Cell-based vaccines
  – Recombinant-based vaccines
  – Antigen-sparing vaccines
  – Improved Influenza Vaccine Manufacturing Initiative
  – Universal vaccines

• Influenza vaccine stockpiling
  – National pre-pandemic influenza vaccine stockpile
  – H5N1 and H7N9 bulk vaccine antigens
  – MF50 and AS03 adjuvants

• Influenza vaccine manufacturing infrastructure & response capability
  – Secure Vaccine Raw Material Supplies
  – Retrofitted & new domestic manufacturing facilities
  – Centers for Innovation in Advanced Development and Manufacturing
  – Fill Finish Manufacturing Network
  – International vaccine manufacturing infrastructure
Influenza Vaccine Development for National Pan Flu Vaccine Goals

Antigen-Sparing Vaccine Technology

Cell-based Vaccines
- H5N1 Vaccine Licensed 04/17/07
- FLUCELVAX® Licensed 11/20/12

Recombinant Vaccines
- Flublok® Licensed 01/16/13

Egg-based Vaccines
- Q-Pan H5N1 Licensed 11/20/2013
- FLUCELVAX® Licensed 11/20/12

Universal Vaccines
- Advanced Development Begins FY15

Manufacturing Improvements
Public-Private Partnerships to Build Domestic Manufacturing Capacity

- Expanding Existing Capacity by Retrofitting Vaccine Manufacturing Infrastructure
  
  **sanofi pasteur – Swiftwater, PA**

- Changing Flu Vaccine Industry
  
  **Novartis – Holly Springs, NC**

2013 ISPE Facility of the Year
True Public-Private Partnership that Changed U.S. Vaccine Industry

First cell-based influenza vaccine mfg. facility in the U.S. (Novartis):

*Dedicated as Pandemic Ready in December 2011*
USG pandemic influenza vaccine policy is two doses for everyone (~ 600 M doses) within 4 months of pandemic onset.
BARDA Expands Flu Vaccine Manufacturing Capacity in Developing Countries

- **Mexico**: Birmex
- **Brazil**: Instituto Butantan
- **South Africa**: Biovac
- **Egypt**: VASERA
- **India**: Serum Institute
- **Vietnam**: IVAC, VABIOTECH, PATH
- **South Korea**: Green Cross
- **Romania**: Cantacuzino Institute, RIBSP
- **Serbia**: Torlak Institute
- **Kazakhstan**: RIBSP
- **Utah State**: N.C. State
- **N.C. State**: State University
- **Mexico**: Birmex
- **Utah State**: N.C. State
- **South Korea**: Green Cross
- **Romania**: Cantacuzino Institute, RIBSP
- **Serbia**: Torlak Institute
- **Kazakhstan**: RIBSP
- **Vietnam**: IVAC, VABIOTECH, PATH
- **South Korea**: Green Cross
- **Brazil**: Instituto Butantan
- **South Africa**: Biovac
- **Egypt**: VASERA
- **India**: Serum Institute
- **Vietnam**: IVAC, VABIOTECH, PATH

**BARDA Training Sites**

- Utah State
- N.C. State
- Mexico
- Birmex

**Licensed/Active Influenza Vaccine Producers**

- America
- Europe
- Asia

**BARDA/WHO Cooperative Agreement Grantees**

- America
- Europe
- Asia

**BARDA/WHO Licensed Pandemic Vaccine for Human Use as of 2013**
BARDA’s Ebola Response is Woven Through Our MCM Programs & Core Service Infrastructure

- CIADMs
- Fill Finish Mfg. Network
- Regulatory & Quality Affairs
- Nonclinical Development Network
- ADS Modeling Hub
- Clinical Studies Network

Years:
- 2006
- 2009
- 2011
- 2012
- 2013
BARDA Assists MCM Developers Directly with Product Development & Manufacturing

CENTERS FOR INNOVATION IN ADVANCED DEVELOPMENT AND MANUFACTURING (CIADM)

Contract Awardees:
Emergent Manufacturing Operations Baltimore LLC
Novartis Vaccines & Diagnostics, Inc.
The Texas A&M University System (TAMUS)
## Ebola Impact as of June 27, 2105

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases</th>
<th>Total Deaths</th>
<th>CFR&lt;sup&gt;1.&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia</td>
<td>10,666</td>
<td>4,806</td>
<td>0.45</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>13,115</td>
<td>3,932</td>
<td>0.30</td>
</tr>
<tr>
<td>Guinea</td>
<td>3,724</td>
<td>2,482</td>
<td>0.67</td>
</tr>
<tr>
<td>Nigeria</td>
<td>20</td>
<td>8</td>
<td>0.40</td>
</tr>
<tr>
<td>Senegal</td>
<td>1</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>DR Congo</td>
<td>70</td>
<td>42</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Total&lt;sup&gt;2.&lt;/sup&gt;</strong></td>
<td><strong>27,596</strong></td>
<td><strong>11,270</strong></td>
<td><strong>0.41</strong></td>
</tr>
</tbody>
</table>

1. CFR=Case fatality rate
2. All Countries
Ebola Vaccine Landscape

**Discovery**
- VEE Replicon and VLP
- Self-amplifying RNA vaccine
- Russian Flu ΔNS1 Vector
- Protein Sciences
- Takeda
- MVA for boost

**Preclinical Development**
- rVSVN4CT1 EBOV
- HuAd6/MVA EBOV
- HuAd6 EBOV
- EBOV GP Nanoparticle
- Rabies EBOV
- VSVΔG EBOV

**Phase I**
- ChAd3 EBOV

**Phase II**
- gsk
- NewLink Genetics
- Merck

**Phase III**
- BARDA
**Ebola Virus Vaccine Vectors**

**Vesicular stomatitis Virus**
- Negative Single Stranded RNA virus
- 5 genes, 11 KB
- Type 1 Transmembrane glycoprotein of Ebola
- Replicating vaccine

http://omicsonline.org/JBTBDimages/2157-2526-S1-004-g002.gif

**Adenovirus**
- Ds DNA
- 22-40 genes
- 26-48 kB
- Non-replicating vaccine
- 7.5 kb potential

http://humanviruses.org/wp-content/uploads/2014/12/Adenovirus_TanTecBiosystems.png

http://omicsonline.org/JBTBDimages/2157-2526-S1-004-g002.gif

**Vaccinia**
- Ds DNA
- 22-40 genes
- 200 kB
- Replicating vaccine or not
- 25 kb potential
Ebola Therapeutics Landscape

**Preclinical Development**
- **IND**

**Phase I**
- **Brincidofovir**
- **Convalescent Sera**
- **ZMapp mAbs**
- **BCX4430**
- **Favipiravir**
- **Brincidofovir**
- **TKM-100802**
- **AVI-7530**
- **Amiodarone**

**Phase II**
- **REGENERON**
- **Genentech**
- **Mapp Biopharmaceutical**
- **Biocryst Pharmaceuticals, Inc.**
- **MediVector, Inc.**
- **Chimerix, Inc.**
- **Tekmira**
- **Sarepta Therapeutics**

**Phase III**
- **BARDA**
- **NIAID**
- **DoD/DTRA**

For Influenza A and B
Ebola mAb Therapeutic
Long Term Strategy

Recent photos from Kentucky BioProducts

• Plant derived antibodies
  – Limited capacity to scale-up
  – Limited number of CMOs
  – No approved products

• CHO cell derived antibodies
  – Enormous capacity to scale-up
  – Many CMOs
  – Many FDA approved products
• BARDA is working with Genentech – expression in mammalian cells
  – Humanizing 13C6 monoclonal and generating a CHO cell line for expression in traditional cell fermentation
  – Potential to be transferred to CIADMs for manufacturing
• BARDA is working with Regeneron – expression in mammalian cells and identification of novel monoclonal antibodies
  – Cloning all three chimeric versions of ZMapp™ antibodies into CHO cells
  – Isolating novel monoclonal antibodies generated from their humanized mouse immunized with inactivated Ebola
• CHO-derived mAbs have been evaluated in NHP, Ebola challenge model (Regeneron) with Genentech planned for June
• Zmapp RCT (Prevail 2)
  — Being run by NIAID, under Master Protocol
  — Cooperation of Ministries of Health and National Universities
  — Clinical grade material from tobacco plants
  — Enrollment of 60 patients in Liberia, U.S., Sierra Leone
  — Plan for starting in Guinea in early July (being shipped this week)
• Tekmira – open label trial halted, futility
• Favipiravir – non-randomized trial, inconclusive data
• Brincidofovir – manufacturer withdrew support
The Ebola Response is Woven Through Our MCM Programs & Core Service Infrastructure
BARDA’s Ebola Response is Global