



# **Processes and Products for Preparation and Response**

## **The Public Health Emergency Medical Countermeasures Enterprise**

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**Assistant Secretary Preparedness and Response**



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# Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)

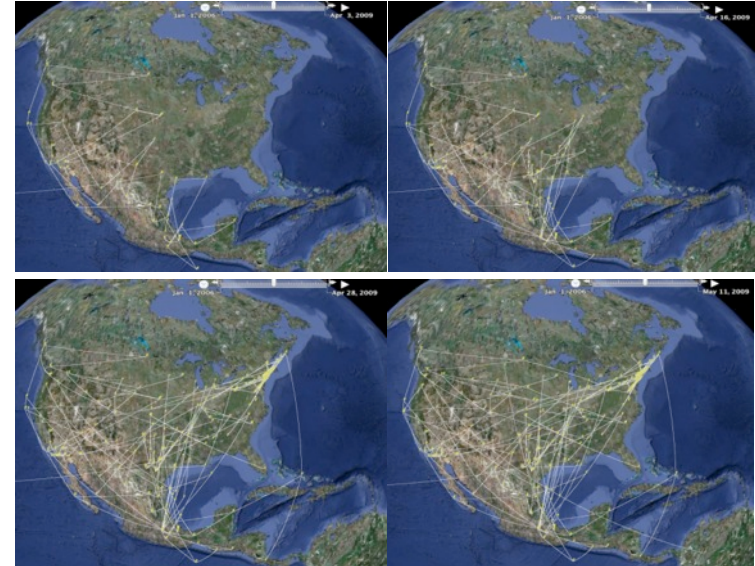


- Federal coordinating body, led by HHS, that protects the U.S. civilian population from national health security threats through the use of medical countermeasures (MCMs)
  - Chemical, biological, radiological, and nuclear agents
  - Emerging infectious diseases (including influenza)
  - Member agencies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

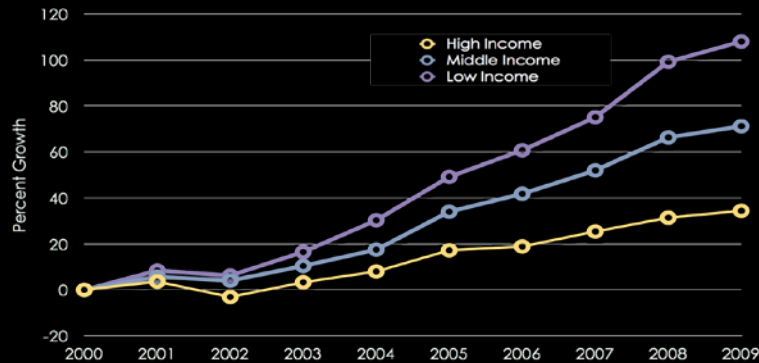


# Globalization and the Reality of Health Security



Credit: Dr. Daniel Janies, Ohio State University  
Early spread of pandemic H1N1 in North America, April-May, 2009

The Future?  
Growth in International Air Traffic Carrying Capacity



Credit: Bio-Diaspora Project

“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

# Biological Defense Must Address a Range of Scenarios

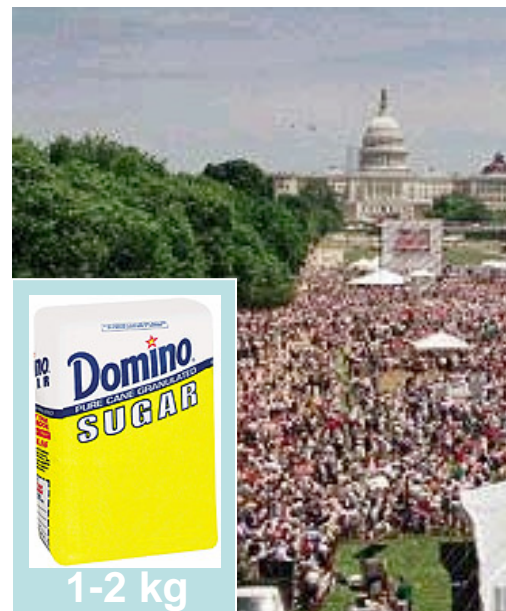
## Low range: 2001 Anthrax Attacks

## Medium range: Aerosol Release



1 gm

via letters



1-2 kg



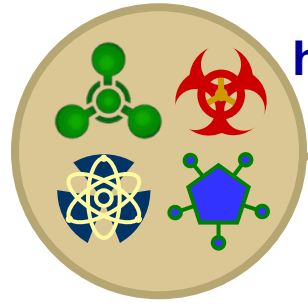
via cropduster

Number that received antibiotic treatment	30,000
Number of illnesses	22
Number of deaths	5
Decontamination	6 Buildings
Direct Economic Cost	>\$1 B

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**



**Complex array of  
Threats**



**Diverse population**

## A Nation Prepared



**Lengthy, risky and  
expensive product  
development**

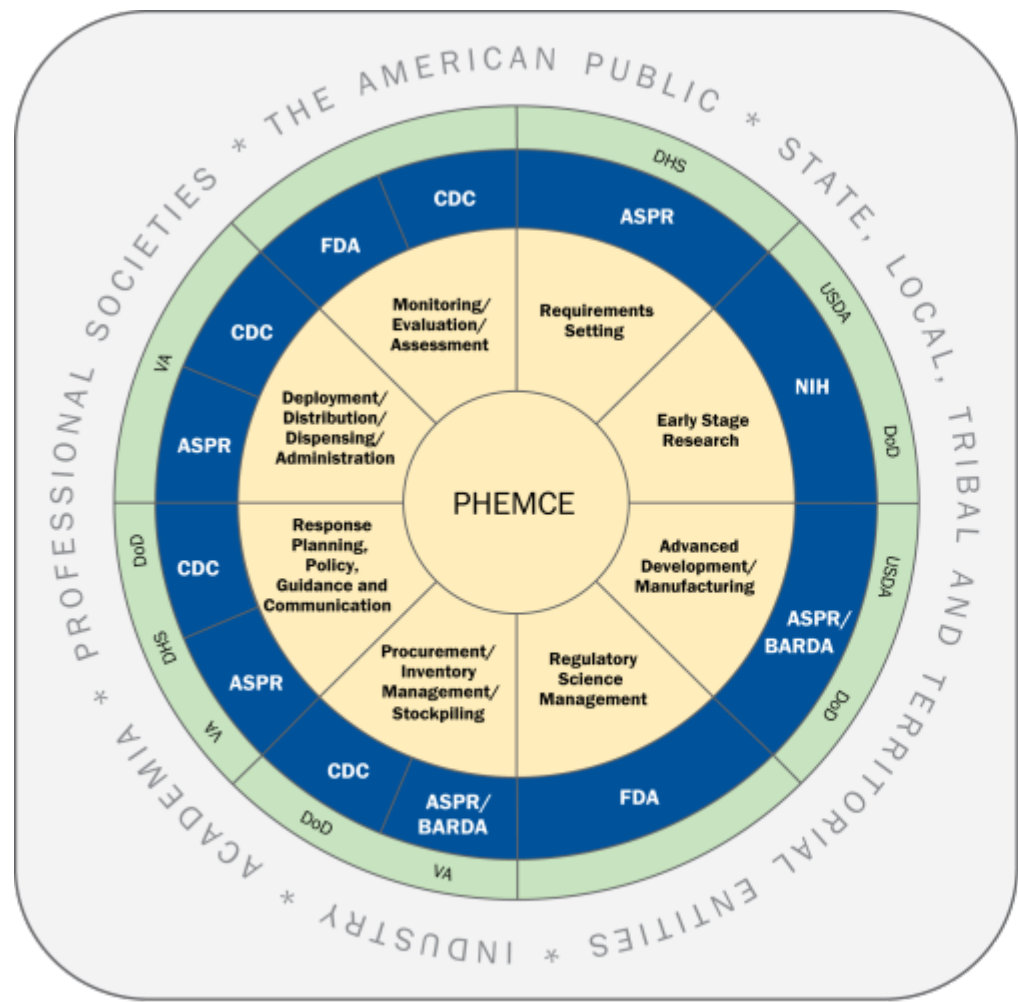


**Prioritize medical  
countermeasure programs  
to effectively address  
mission goals**



**Strategies &  
dependencies for  
effective use**

# PHEMCE Lead Roles



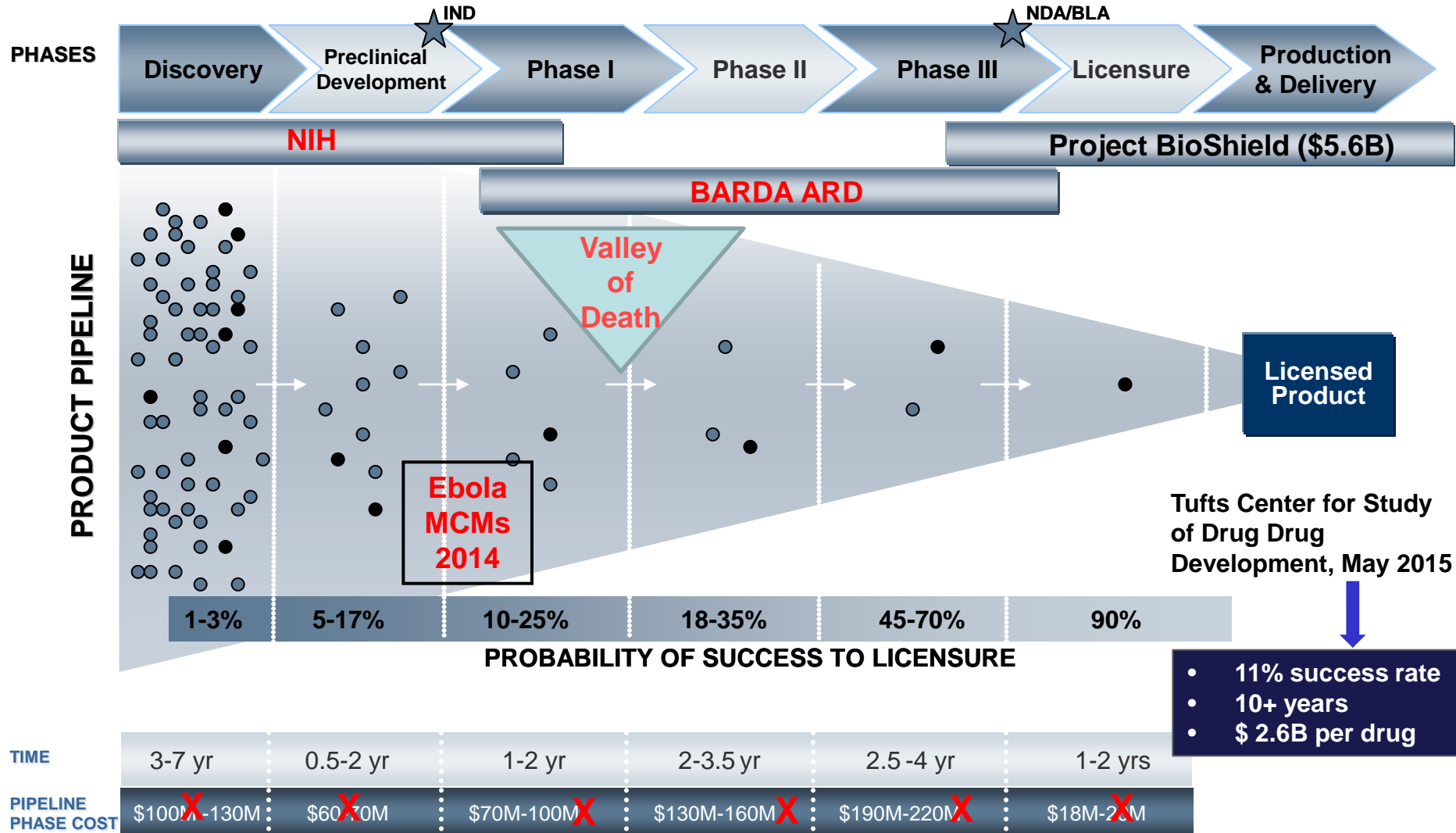
### Key

- 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

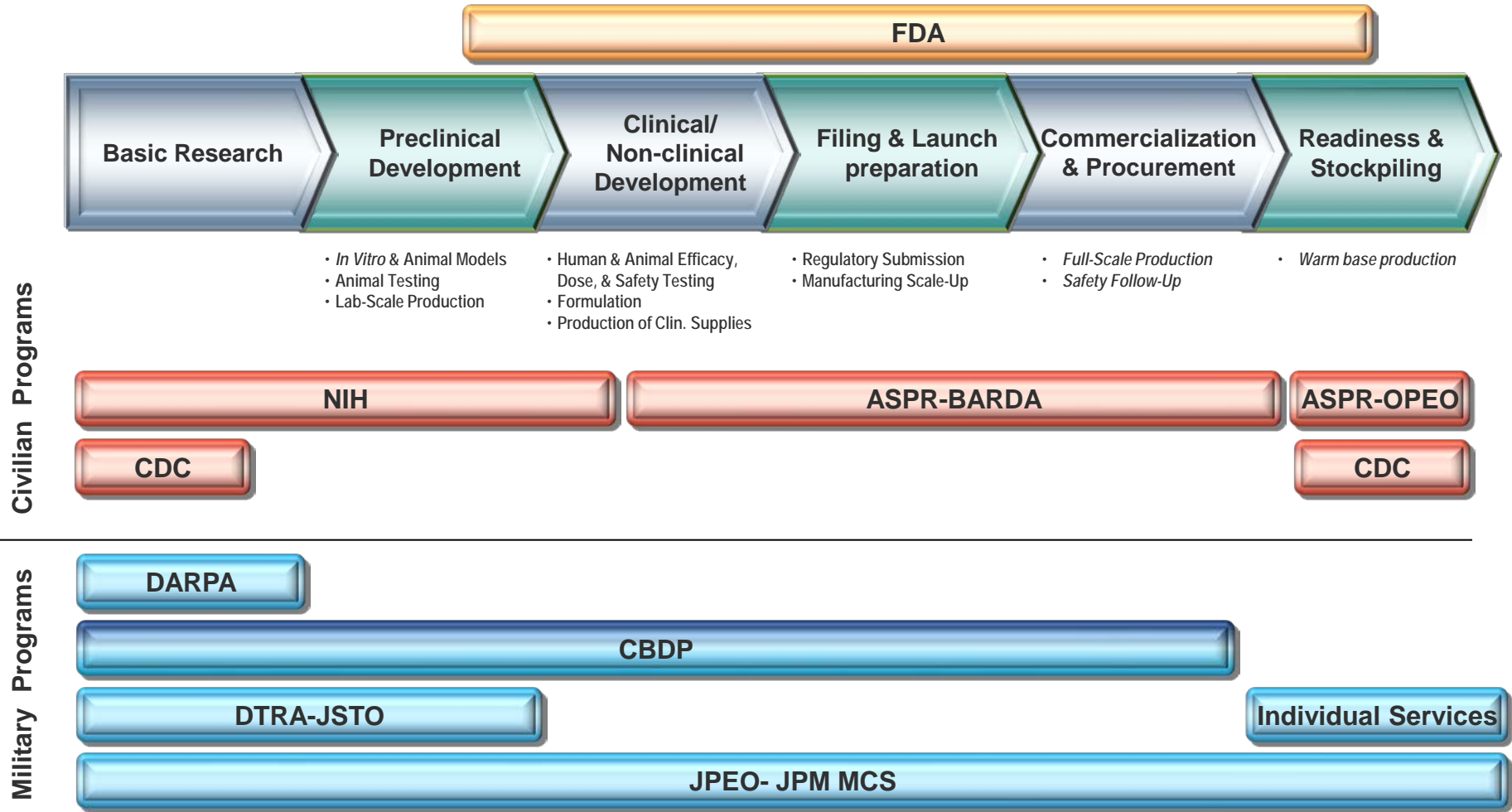
# Ebola Vaccine & Drug Development is Still Expensive, Lengthy, & Risky







# No Single Agency has Visibility into the Entire MCM Development Portfolio





# 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 (melioidosis)
  - 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.



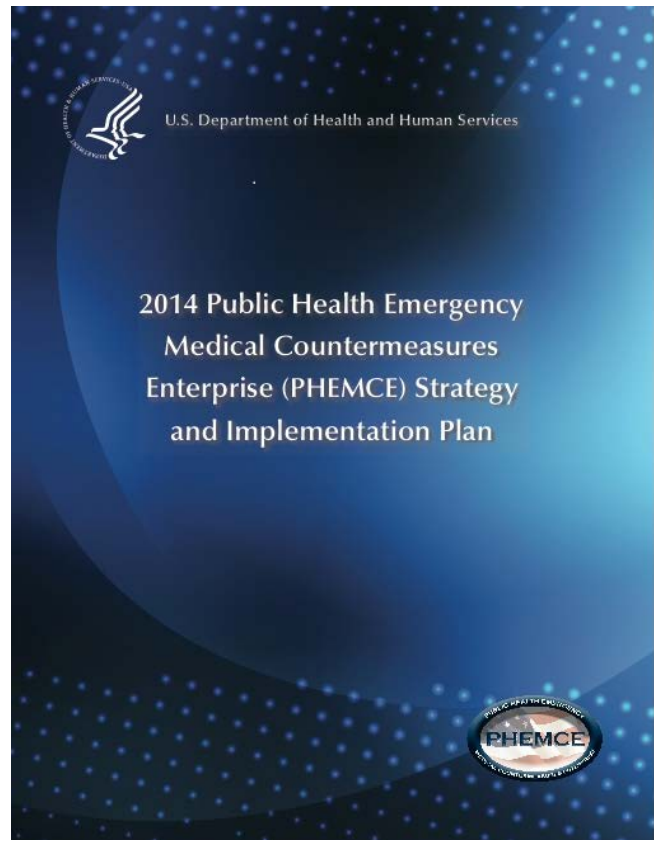
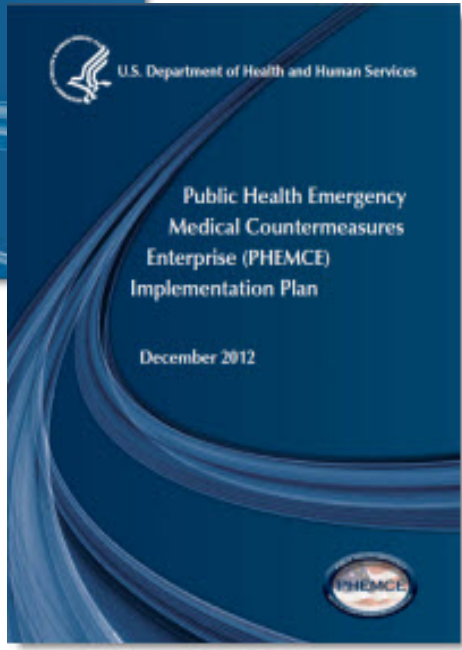
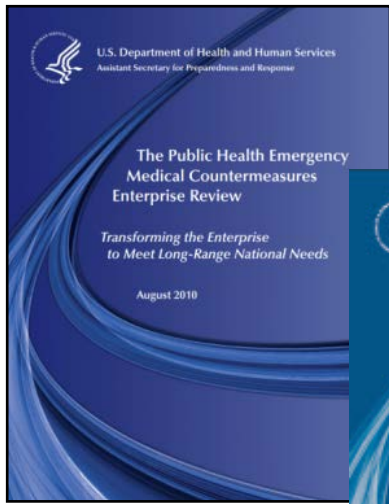
# The Evolution of the PHEMCE



- 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>
- Recognized in 2013 reauthorization of the Pandemic and All-Hazards Preparedness Act for specific deliverables



# Key PHEMCE Documents





# PHEMCE Prioritization Framework



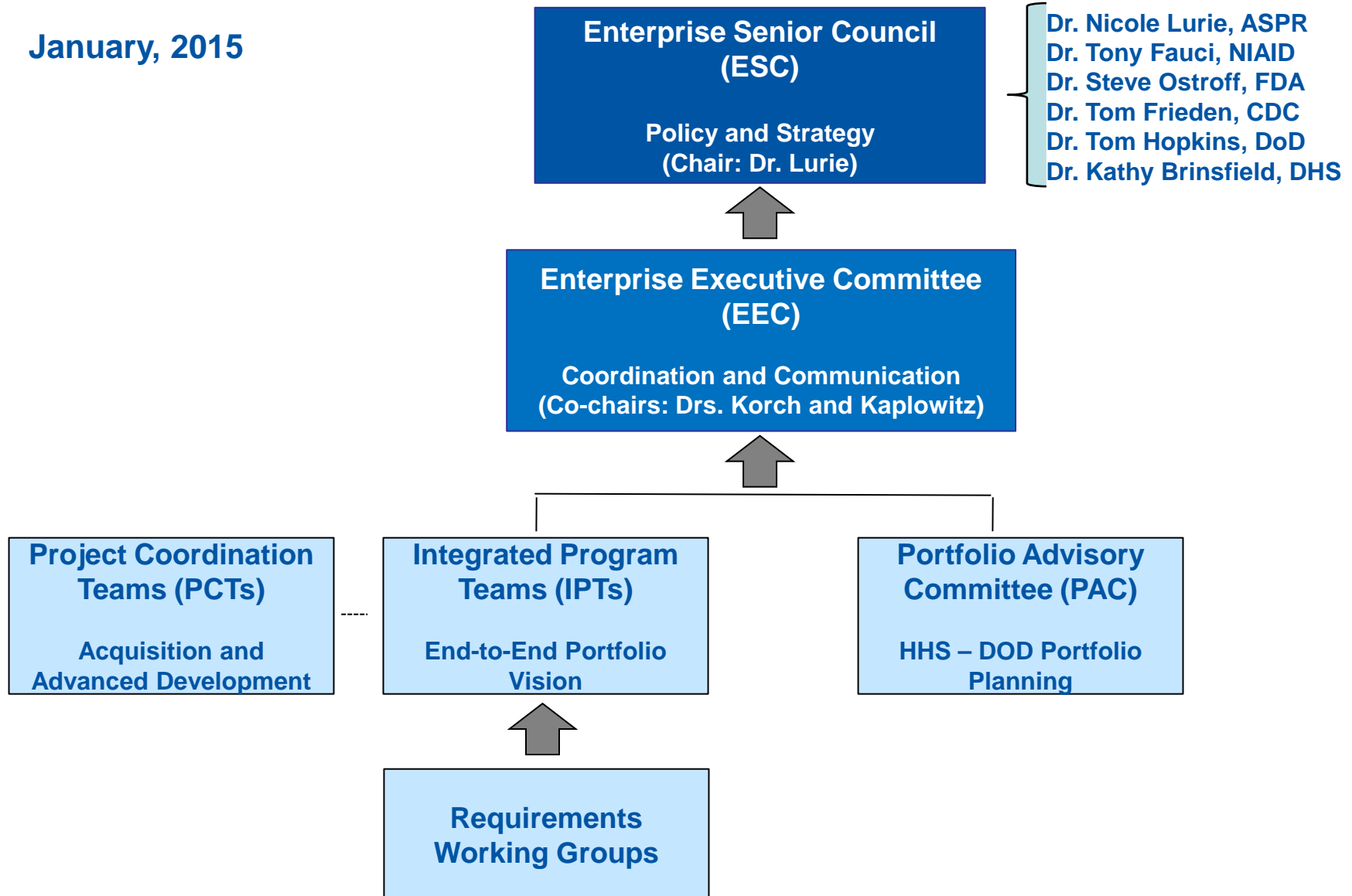
- All Actions in PHEMCE are based on Two Core Principles
  - Limit adverse health impact
  - Stewardship of resources that create an enduring capability
- Product decisions will be judged against these criteria:
  - Focused on key threats
  - Potential for multi-functional product
  - Forecasts operational 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



January, 2015





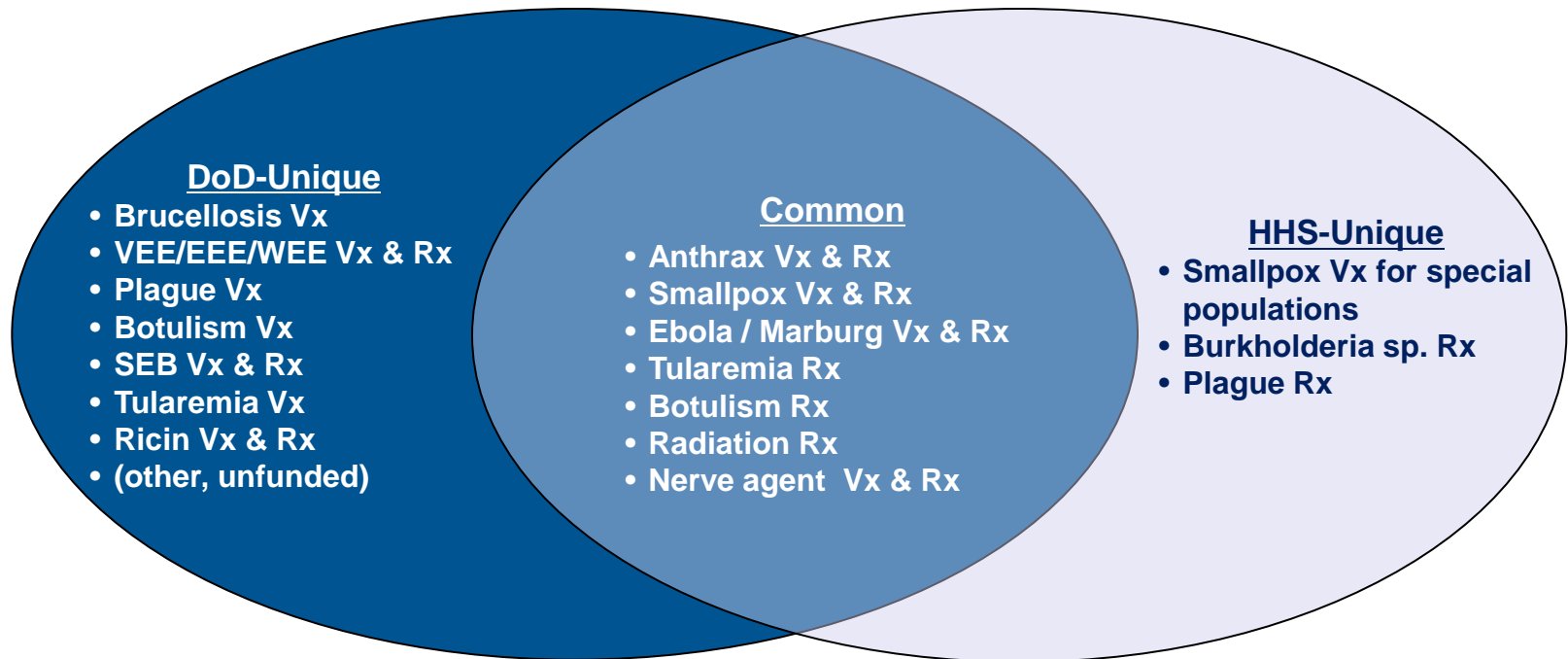
# PHEMCE Integrated Program Teams (IPTs)



- 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**



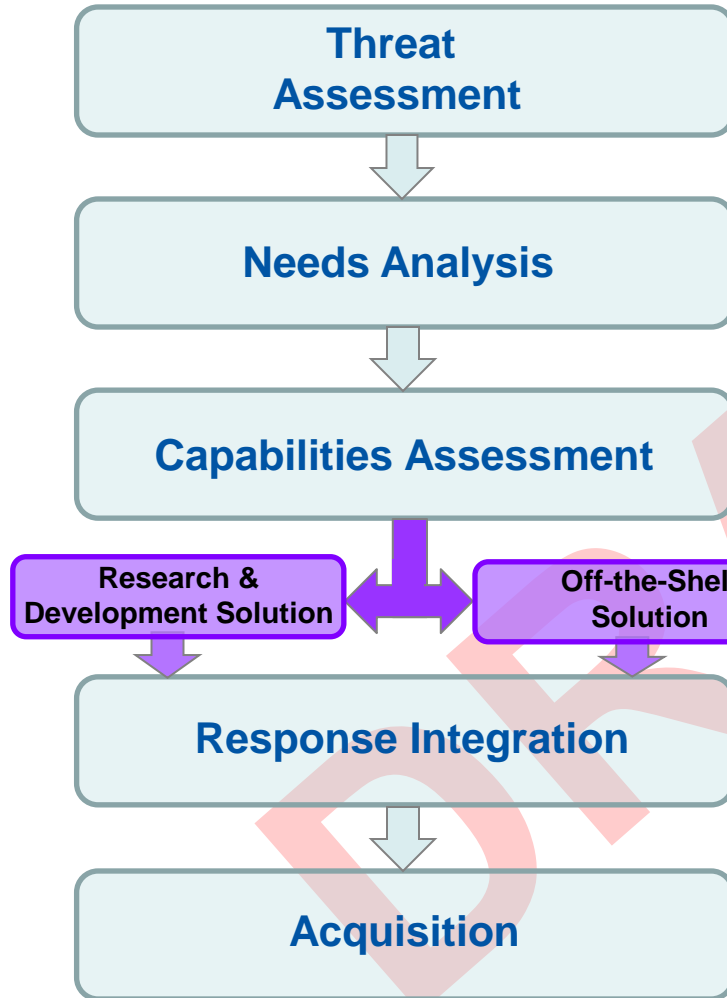
# Integrated Portfolio for CBRN MCM: Requirements – Unique and Convergent



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



# Incorporating Capabilities into PHEMCE CBRN Requirements Architecture



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	AD Priorities Through FY17 <sup>1</sup>	Current HHS Holdings <sup>2</sup>	Procurements Programmed Through FY13 <sup>3</sup>	Additional Procurements Projected Through FY17 <sup>4</sup>
Anthrax Antitoxin	X	X	SRF <sup>5</sup>	TBD <sup>6</sup>
Anthrax Vaccine	X	X	DSNS <sup>7</sup>	DSNS, TBD
Botulism Antitoxin	X	X		
Broad Spectrum Antimicrobials	X	X <sup>8</sup>	DSNS	DSNS, TBD
Cyanide Antidote	X	X		DSNS
Diagnostics – Bioassay	X			
Diagnostics – Biodosimetry	X			TBD
Diagnostics – Biological Agents	X			
Diagnostics – Pandemic Influenza	X			
Diagnostics – Volatile Nerve Agents	X			
Nerve Agent Antidote	X	X	DSNS, SRF	DSNS
Nuclear Agents – Acute Radiation Syndrome (ARS) – Gastrointestinal (GI), Skin, and/or Lung Therapeutics	X			TBD
Nuclear Agents – ARS – Hematopoietic Therapeutics	X	X	SRF	
Nuclear Agents – Thermal Burn Therapeutics	X	X	DSNS	TBD
Pandemic Influenza Antivirals	X	X	DSNS	DSNS
Pandemic and Pre-Pandemic Influenza Vaccine	X	X		
Patient (Chemical) Decontamination	X			
Radiological Agents – Decorporation/Blocking Agents	X	X	DSNS	DSNS, TBD
Respiratory Protective Devices	X			DSNS
Smallpox Antivirals	X	X	SRF	
Smallpox Vaccine	X	X	DSNS, SRF	DSNS, TBD
Ventilators	X	X	DSNS	
Viral Hemorrhagic Fever Antivirals	X			
Viral Hemorrhagic Fever Vaccine <sup>9</sup>				

**Footnotes:**

- <sup>1</sup> These priorities include new products coming through the advanced development pipeline, as well as enhancements to current products in the SNS.
- <sup>2</sup> Includes inventory held in both the SNS and alternative stockpiles
- <sup>3</sup> Contingent upon available resources
- <sup>4</sup> Assuming appropriations are available to maintain currently stockpiled and programmed levels
- <sup>5</sup> Solicitations are ongoing to maintain existing preparedness levels and manufacturing capacity established under previous contracts.
- <sup>6</sup> To Be Determined - Purchase of medical countermeasures under Project BioShield are planned pending appropriations
- <sup>7</sup> 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.
- <sup>8</sup> This includes antimicrobials for the following threat agents: anthrax, plague, tularemia, typhus, and secondary infections resulting from radiological and nuclear agents or pandemic influenza.
- <sup>9</sup> 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)."

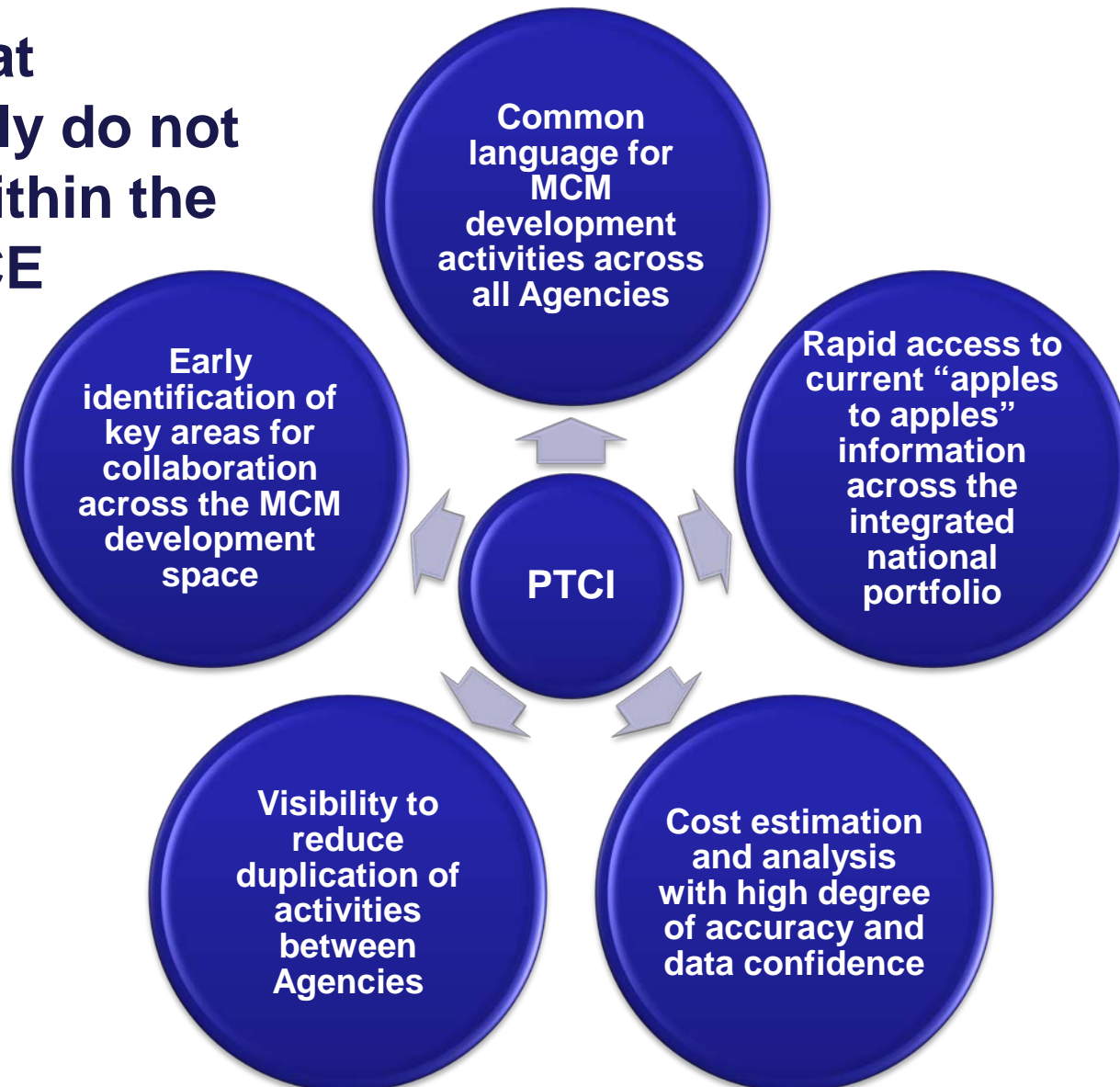


# Portfolio Tracking Tool an HHS-DOD Partnership



- 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

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







## 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

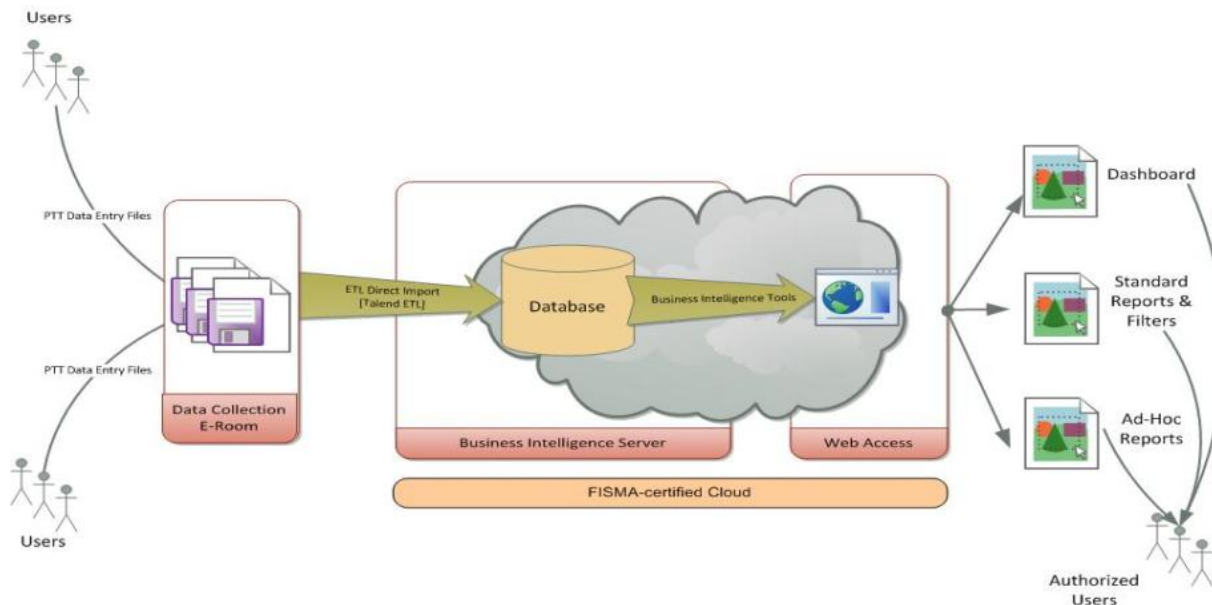
- Contract data
- Indication being pursued
- Requirement being supported
- Contracting types, SBA Info (small business)
- Funding Types (Color of money)
- And Others as required by stakeholders

### Portfolio Level Output

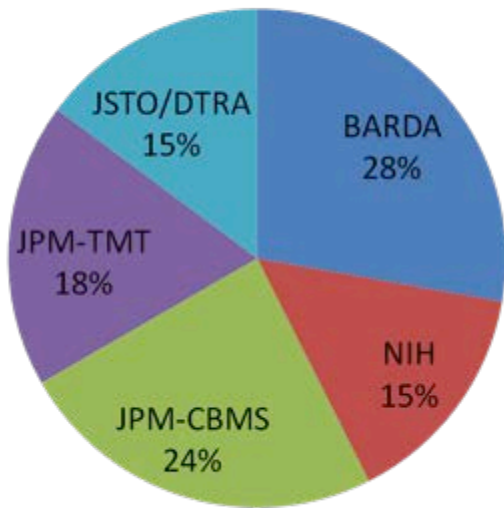
A business intelligence analytics and reporting engine will allow for custom dashboards and reports as well as *ad hoc* analytics and reporting.

- Benchmarking
- Risk management
- Resource demand
- Investments by threat
- Pipeline maturity
- Budget allocation
- Budget and resource planning
- Strategic alignment
- Performer analysis
- Agency-specific SBA Reports

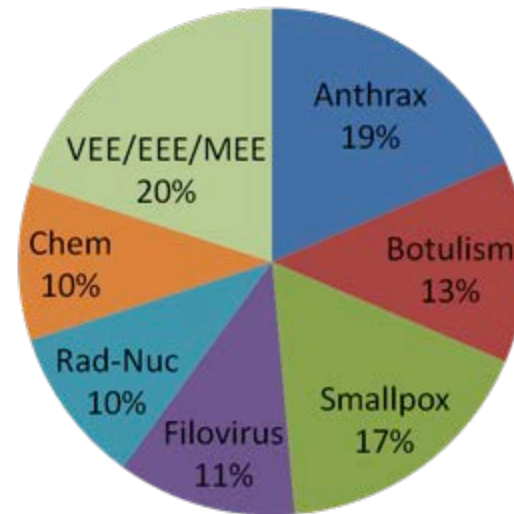
**This system is enabling real-time web-based data hosting, upload, analytics and reporting. For the first time all PHEMCE data is commonly structured, consolidated and available for analysis down to the individual contract level.**



### Overall Spending on MCM by Agency



### Overall Spending by Threat Area





# 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



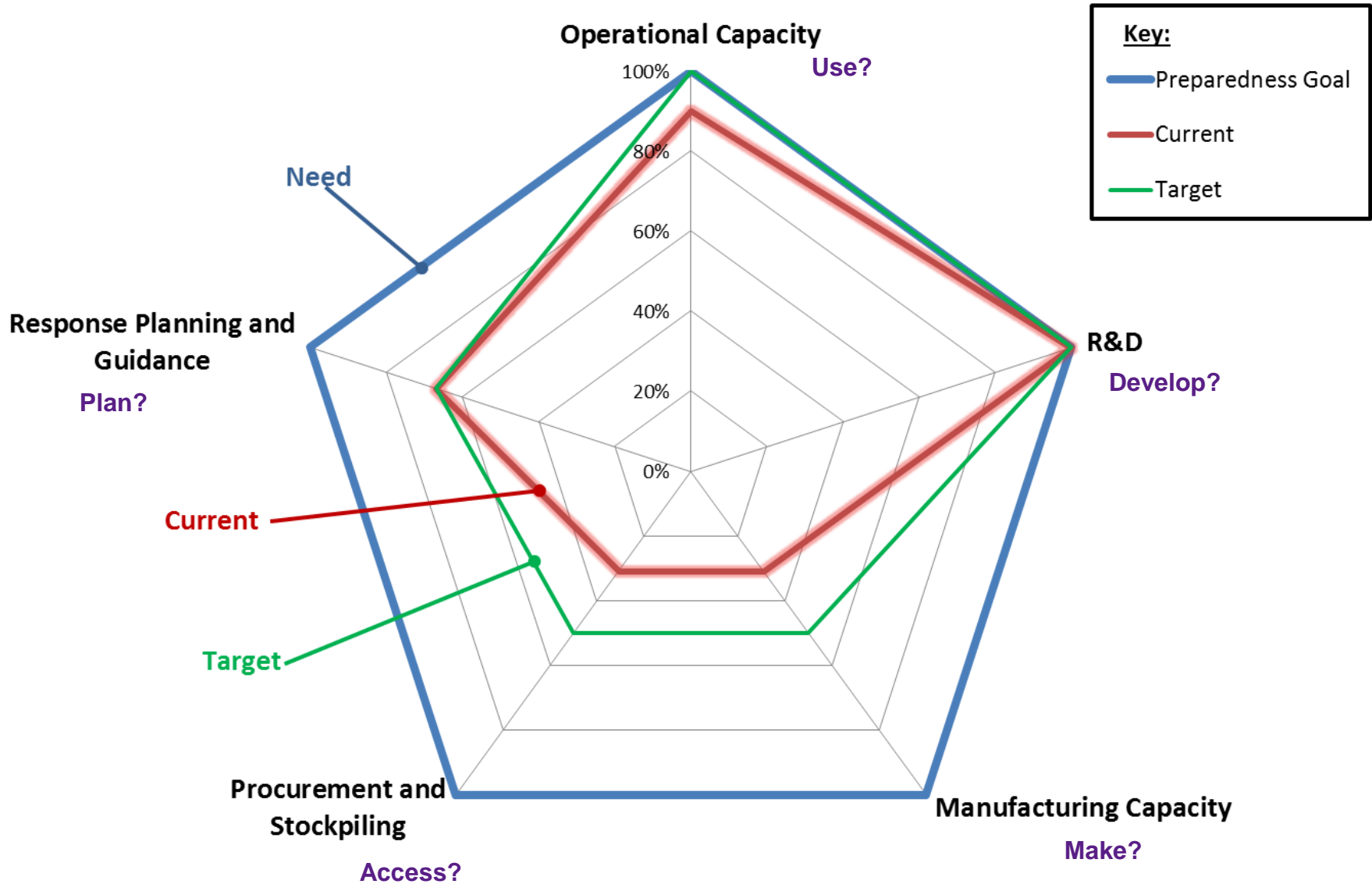
# Preparedness Goal Determinants



- 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





# Biomedical Advanced Research and Development Authority (BARDA)

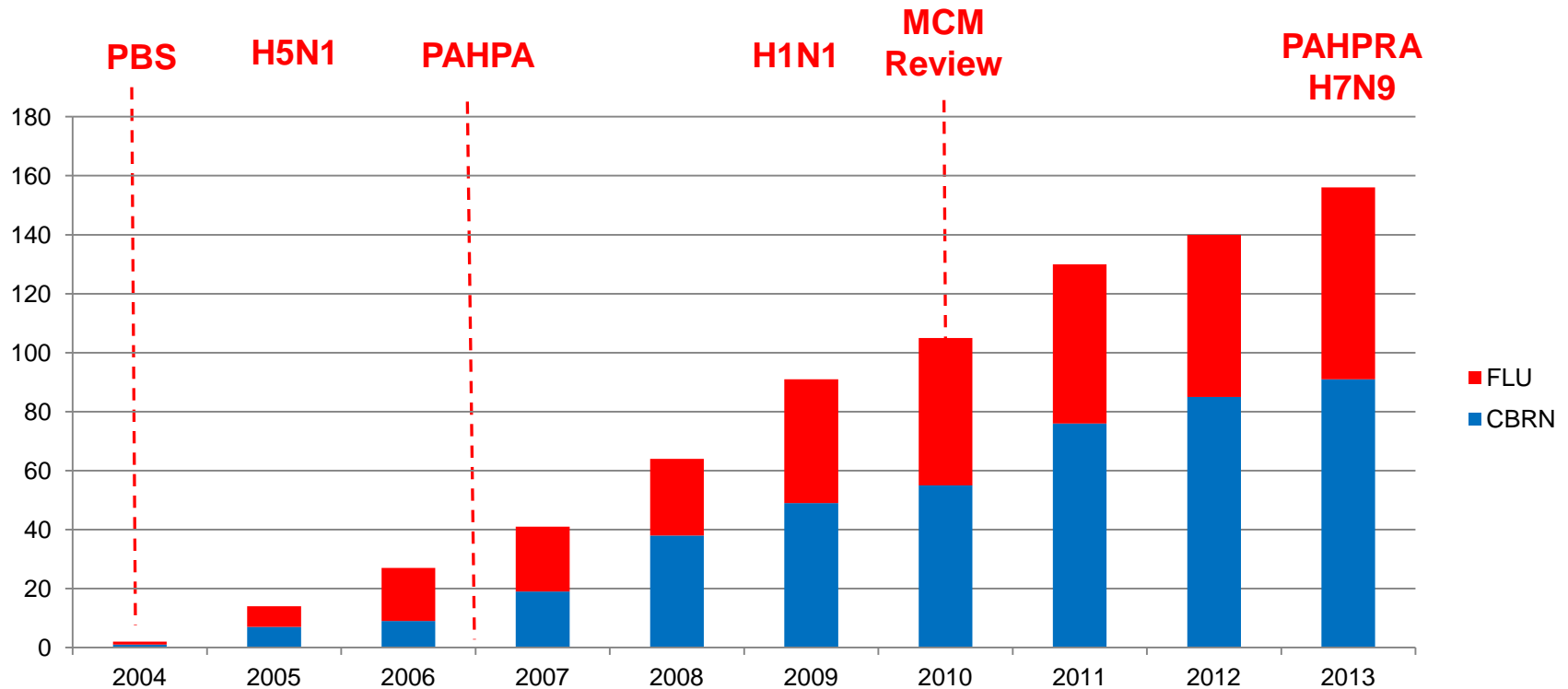




# BARDA Created a Robust & Productive MCM Development Pipeline



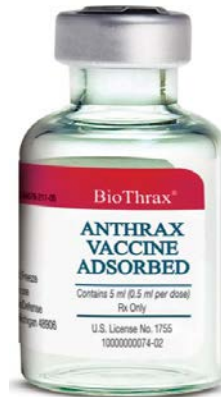
- More than 150 MCM product candidates in development since 2004



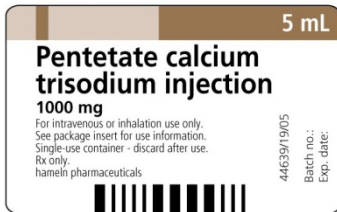
# BARDA MCMs under Project BioShield



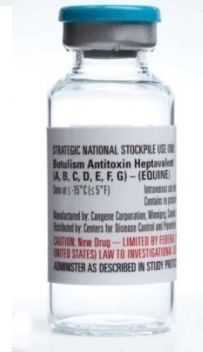
**Smallpox**



**Anthrax**



**Radiation**



**Botulism**



**Chemical**





# 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)**

# BARDA MCMs... *Crossing the Finish Line* 2012-2014 FDA Approvals

## Cell-based Influenza Vaccine



*Novartis*

## Recombinant-based Influenza Vaccine



*Protein Sciences Corp.*

## Influenza IV Antiviral Drug



## Anthrax Antitoxin



*HGS/GSK*

## H1N1 & H5N1 Vaccine w/ Adjuvant



*GlaxoSmithKline*



## Botulinum Antitoxin



*Cangene*

## Next-Gen Portable Ventilators



*Covidien*

## Flu/RSV POC Diagnostic

*3M/Focus*





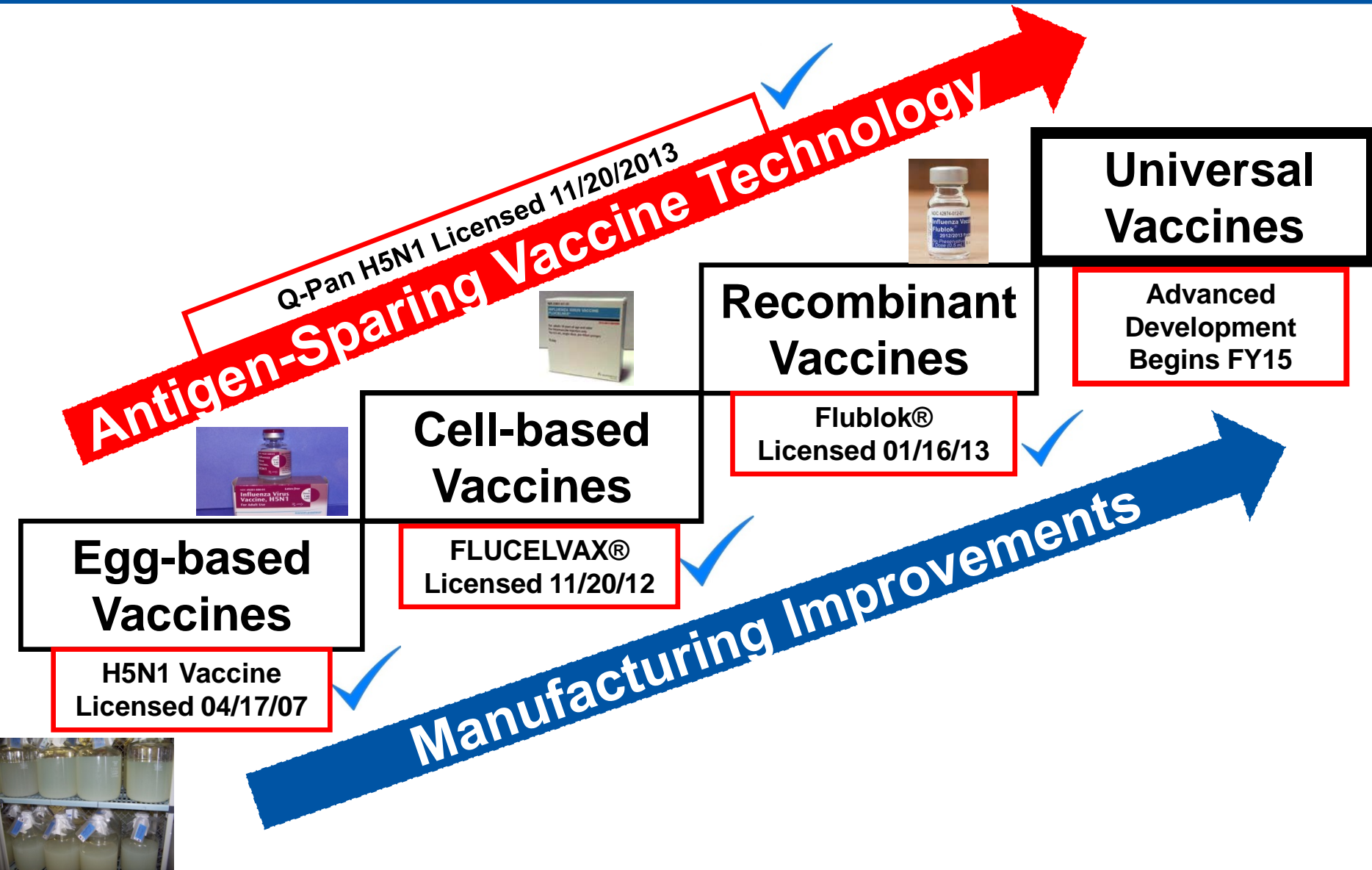
# BARDA Influenza Vaccine Strategies



- **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



- Expanding Existing Capacity by Retrofitting Vaccine Manufacturing Infrastructure



**sanofi pasteur – Swiftwater, PA**

- Changing Flu Vaccine Industry



**2013 ISPE Facility of the Year**

**Novartis – Holly Springs, NC**

# True Public-Private Partnership that Changed U.S. Vaccine Industry

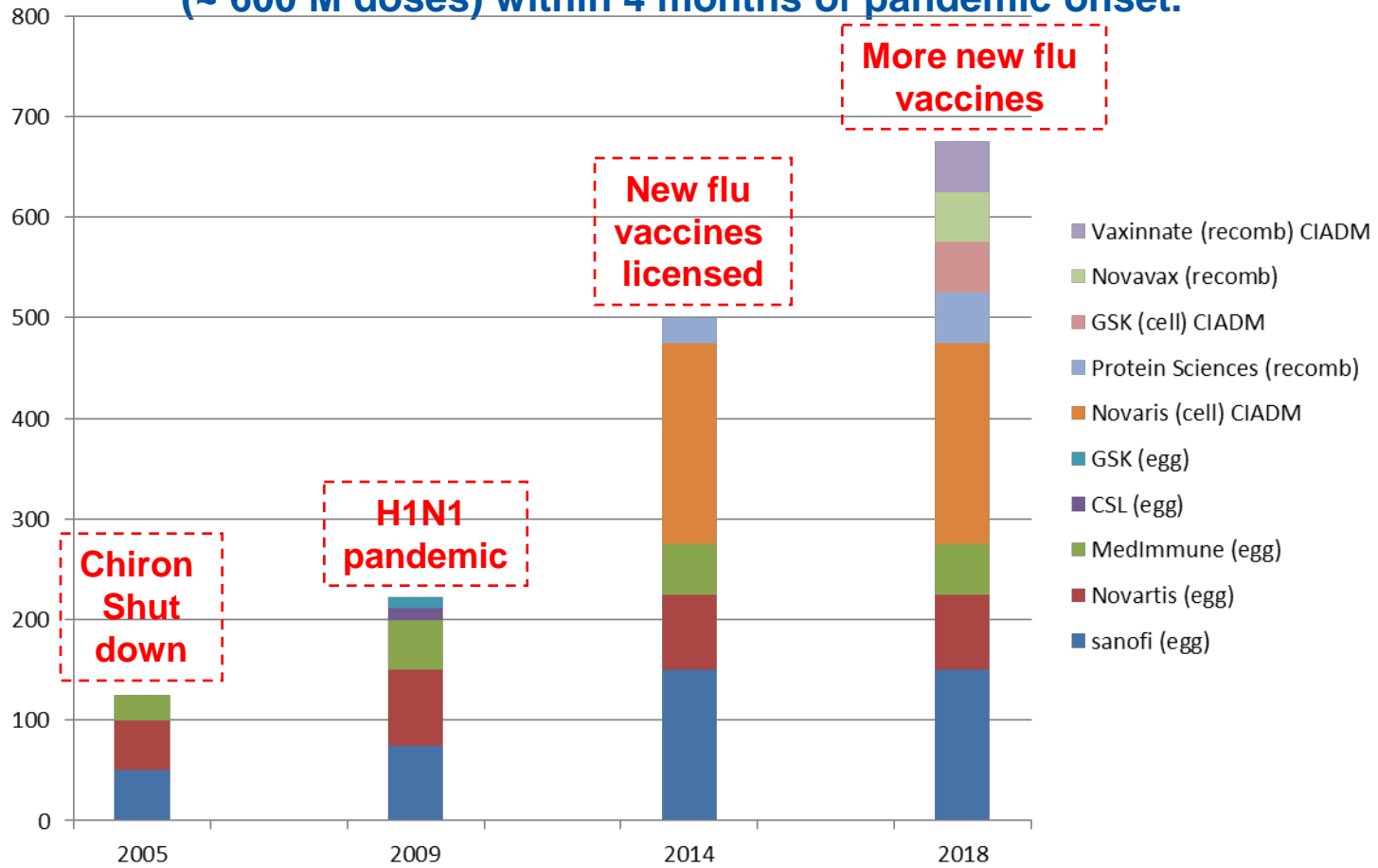


**First cell-based influenza vaccine mfg. facility in the U.S. (Novartis):  
*Dedicated as Pandemic Ready in December 2011***

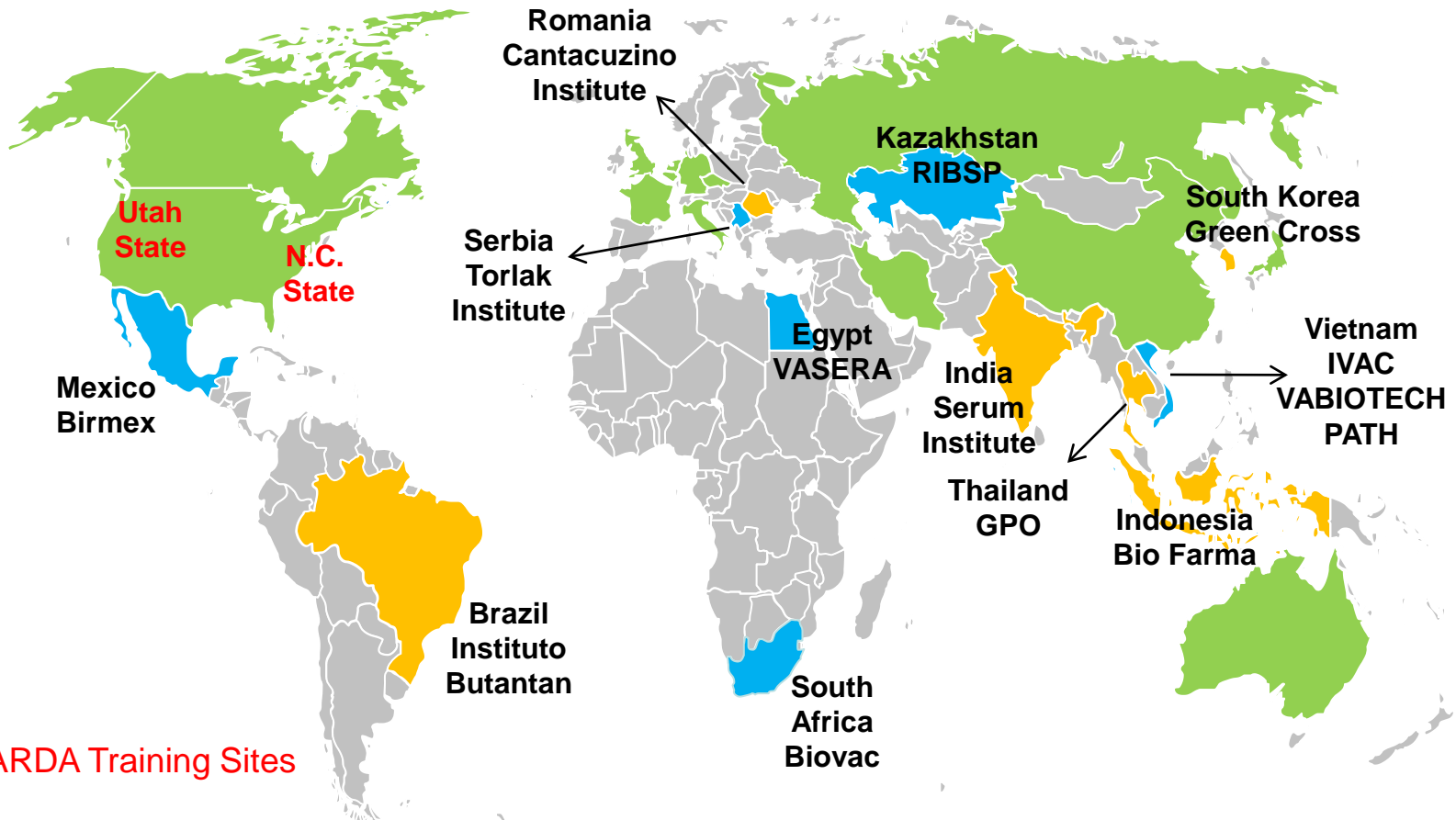


# Assemble manufacturing network with sufficient capacity

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



- BARDA Training Sites
- Licensed/Active Influenza Vaccine Producers
- BARDA/WHO Cooperative Agreement Grantees
- BARDA/WHO Licensed Pandemic Vaccine for Human Use as of 2013



# BARDA's Ebola Response is Woven Through Our MCM Programs & Core Service Infrastructure



## CENTERS FOR INNOVATION IN ADVANCED DEVELOPMENT AND MANUFACTURING (CIADM)





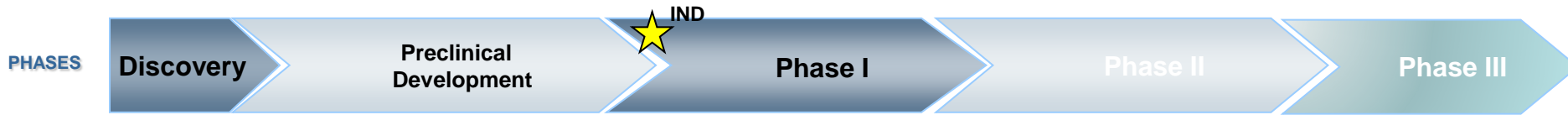
# Ebola Impact as of June 27, 2105



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

1. CFR=Case fatality rate
2. All Countries

# Ebola Vaccine Landscape



**USAMRIID**  
United States Army  
Medical Research Institute  
of Infectious Diseases  
BioDefense solutions to protect our nation

VEE Replicon and VLP

**NOVARTIS**

Self-amplifying RNA vaccine

**Russian  
Flu ΔNS1 Vector**

**Protein  
Sciences**

**Takeda**

**emergent**  
biosolutions™

MVA for boost

**PBS**  
Profectus BioSciences, Inc.

**rVSVN4CT1  
EBOV**

**VAXART**

**HuAd6  
EBOV**

**Jefferson**  
THOMAS JEFFERSON UNIVERSITY

**Rabies EBOV**

**Crucell**

**BAVARIAN NORDIC**

**HuAd6/MVA  
EBOV**

**NOVAVAX**  
Creating Tomorrow's Vaccines

**EBOV GP  
Nanoparticle**

**gsk**

**ChAd3 EBOV**

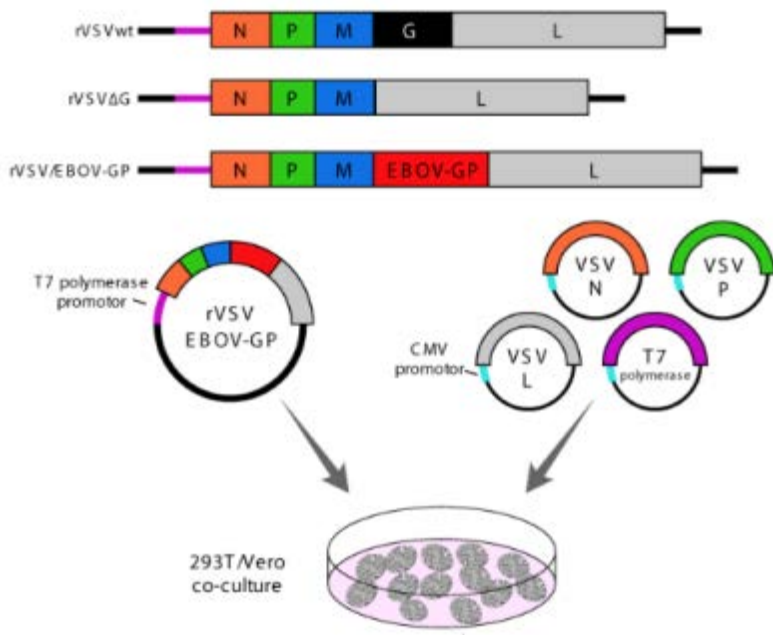
**NewLink  
GENETICS**

**MERCK**  
Be well

**rVSVΔG EBOV**

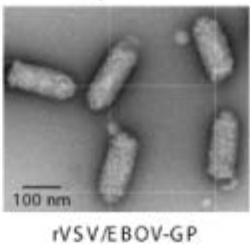
**BARDA**

# Ebola Virus Vaccine Vectors



## Vesicular stomatitis Virus

Negative Single Stranded RNA virus  
5 genes, 11 KB  
Type 1 Transmembrane glycoprotein of Ebola  
Replicating vaccine



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

### Vaccinia

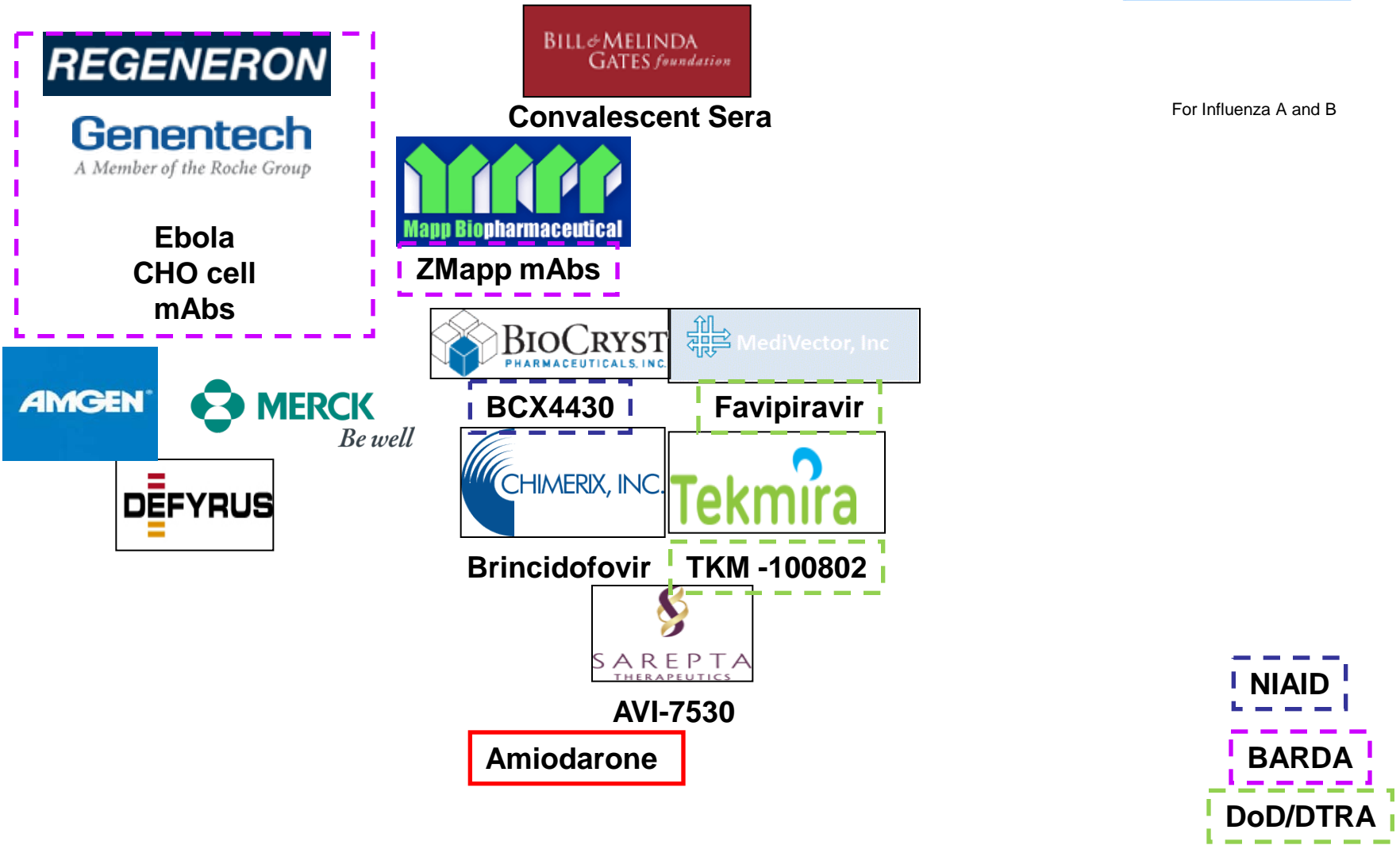
Ds DNA  
 22-40 genes  
 200 kB  
 Replicating vaccine or not  
 25 kb potential

Size of particle: 360 x 270 x 250 nm

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



# Ebola Therapeutics Landscape





# 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

# Therapeutic – mAbs Produced in CHO Mammalian Cells

- 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





# Therapeutics Clinical Trials



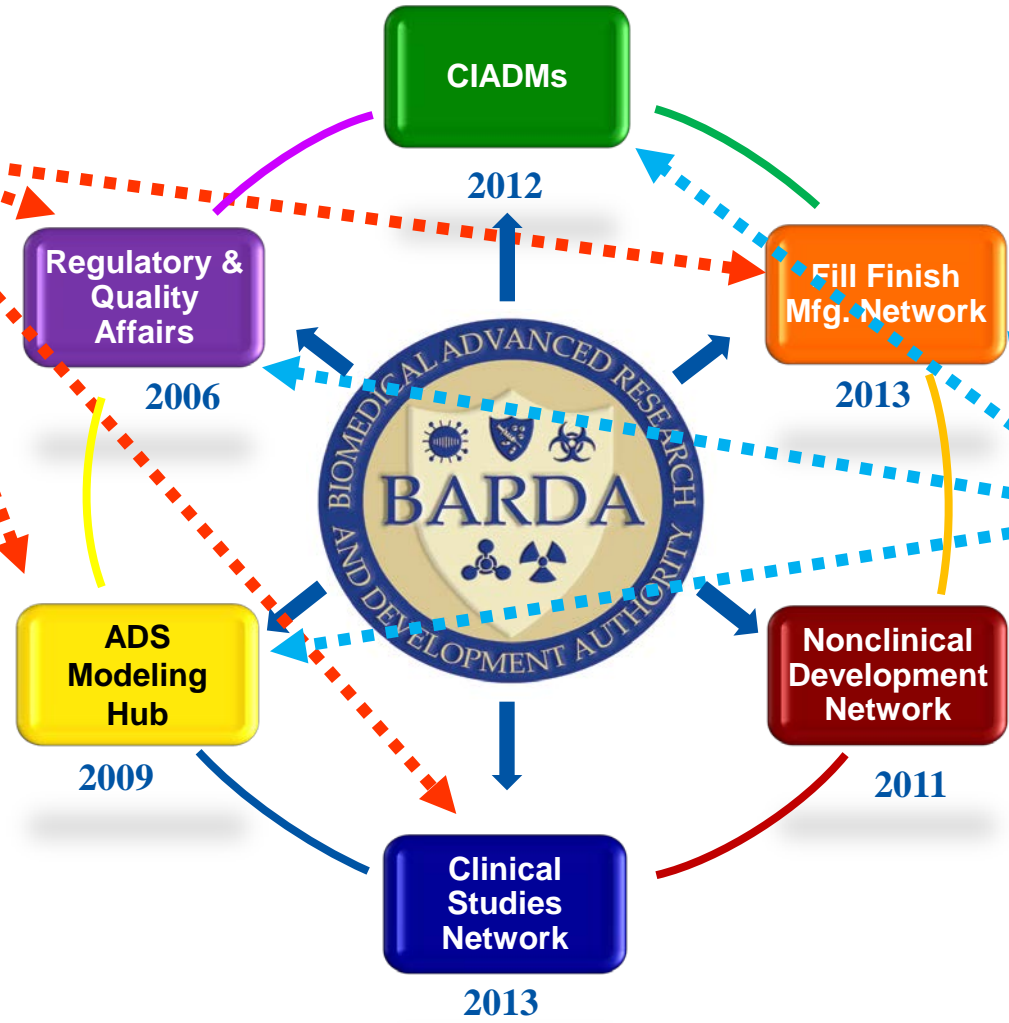
- Zmapp RCT (Prevail 2)
  - Being run by NIAID, under Master Protocol
  - Cooperation of Ministries of Health and National Universities
  - Clinical grade material from tobacco plants
  - Enrollment of 60 patients in Liberia, U.S., Sierra Leone
  - Plan for starting in Guinea in early July (being shipped 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



**Ebola Vaccines**



**Ebola Therapeutics**



# BARDA's Ebola Response is Global

