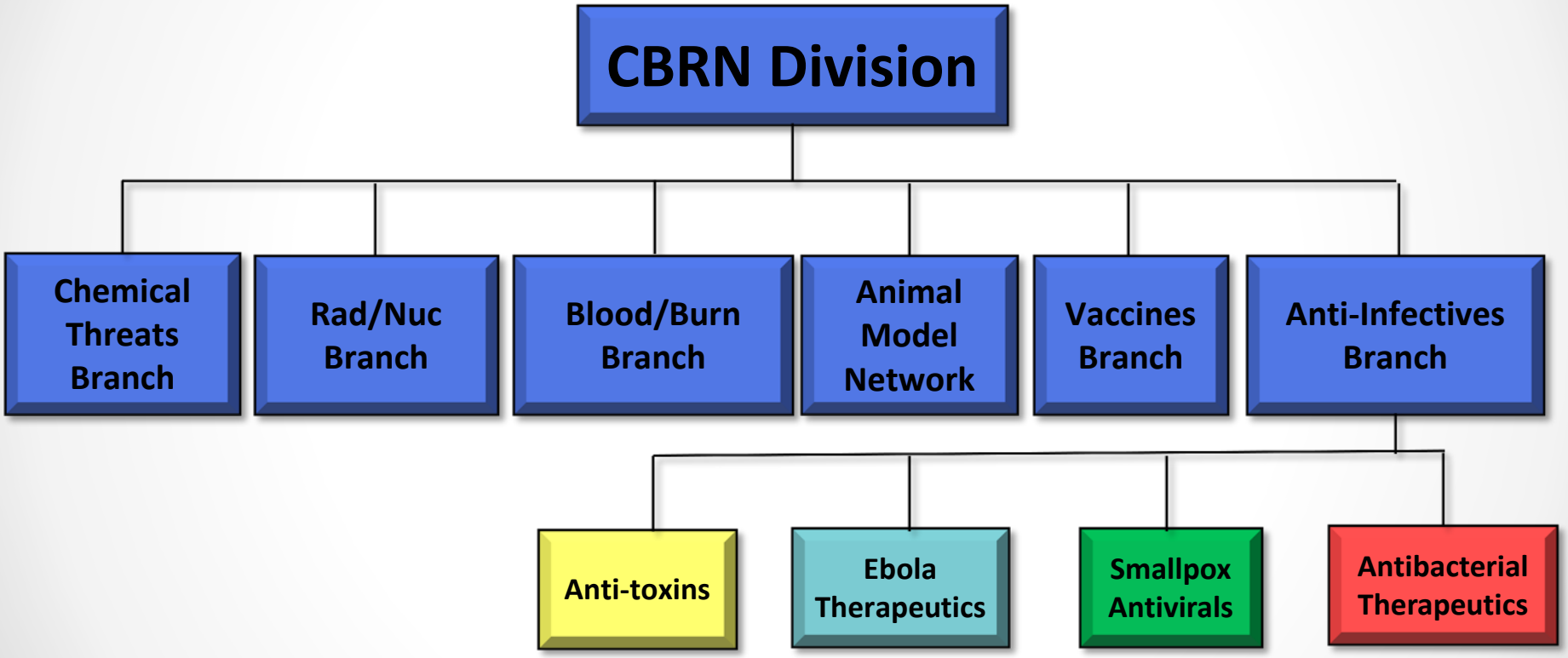
ANTI-INFECTIVES PROGRAM

Melissa Stundick,
PhD October 14,
2015

Resilient People. Healthy Communities. A Nation Prepared.

Organization Chart



Partner Companies

Anti-toxin Program

- Botulism Anti-toxin
  - Objective: Develop safe and effective botulism antitoxin to treat botulism intoxication
  - BAT™ approved in March 2013
  - Stockpiling goals achieved

- Anthrax Anti-toxin
  - Objective: Develop safe and effective anthrax antitoxins to treat inhalational anthrax
  - Raxi approved Dec 2012
  - AIG approved 2015
  - Anthim BLA submitted Mar 2015
  - Stockpiling preparedness goals achieved

Anti-toxin Program

- Future Focus
  - Sustainment and risk mitigation
  - Complete post marketing commitments

- BAA Area of Interest #2.1:
  - 2.1 Development of peptide or small molecule antitoxins, and other novel compounds, with innovative formulations offering enhanced long-term stability. The candidate must be at TRL-6 (active IND and human safety data).

Smallpox Antiviral Program

- BARDA has a requirement for 1.7M treatment courses of smallpox antiviral for use in individuals presenting symptomatic smallpox
- Two ongoing programs, aligns with IOM recommendation and PHEMCE goal for two antiviral drugs with different mechanisms of action

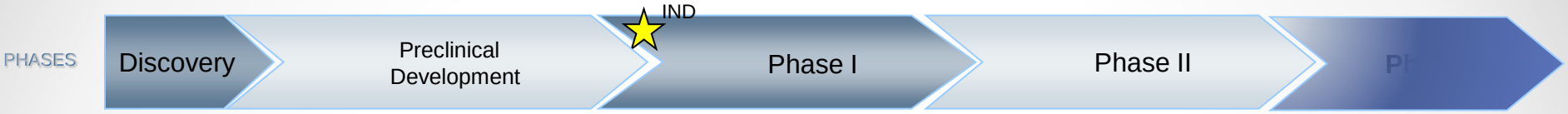
Product	Biothreat Spectrum	Commercial Indications	Class	Development Phase
ST-246/TPOXX	Smallpox	None	Novel, viral egress	Phase III
CMX-001/ Brincidofovir	Smallpox	dsDNA virus infections	Nucleoside analog	Phase III

Future Trajectory of the Smallpox Antiviral Program

- Support ongoing programs through FDA approval
- Fulfill stockpiling goals
- Transition focus to sustainment and fulfillment of post marketing commitments

Ebola Therapeutics Landscape

Summer 2014



Bill & Melinda Gates foundation

Convalescent Sera

Tekmira

TKM -100802

DEFYRUS

Zmab mAbs

Mapp Biopharmaceutical

ZMapp mAbs

BioCryst Pharmaceuticals, Inc.

BCX4430

SAREPTA THERAPEUTICS

AVI-7530

CHIMERIX, INC.

Brincidofovir for CMV/Adno

MediVector, Inc

Favipiravir for influenza

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Ebola Therapeutics Landscape

Current

Other Ebola mAbs

TKM -100802

Convalescent Sera

Pichia platform

AVI-7530

Zmab mAbs

ZMapp™ mAbs

BCX4430

Brincidofovir for CMV/Adno

BARDA Funded

REGN3477-70-71

Mil-77

Favipiravir for influenza

hZMapp mAbs

Trichoderma platform

ZMapp Program

- Mapp Contract: ZMapp™ is currently being manufactured at KBP (Kentucky BioProcessing)
  - Manufacturing in tobacco plants starting in August 2014
  - Three monoclonal antibodies that bind to the Ebola glycoprotein
  - Transitioned from DoD and NIAID discovery and early development
  - Six manufacturing campaigns completed to date
  - Additional six manufacturing campaigns – initiated July 2015
  - Phase 3 efficacy study in West Africa and U.S. under the Common Master Protocol started in Feb. 2015

- Medicago and Fraunhofer producing ZMapp™ monoclonal antibodies using their own tobacco plant expression systems
  - Alternative plants and expression system
  - Evaluate activity of ZMapp-like mAbs vs. ZMapp in animal challenge studies

Mapp Biopharmaceutical

Ebola mAb Therapeutic Long Term Strategy

- 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

Regeneron Program

- Regeneron has a platform technology to quickly identify novel, mAbs in a murine system and convert to fully human antibodies
- Regeneron is developing a novel 3 mAb cocktail produced in CHO cells
- BARDA awarded a contract to Regeneron in September 2015 to support manufacturing, assay development, IND enabling studies
- Regeneron mAb cocktail has shown efficacy in NHPs when administered 5 dpi
- Regeneron will collaborate with NIH to evaluate mAb cocktail in Phase 1 studies

Biocryst – BCX4430

- BCX4430 is an adenosine analog with activity against Marburg and Ebola viruses
- BARDA/NIAID collaboration to support product development
- BARDA is supporting manufacturing, in vitro and nonclinical toxicology studies
- NIAID funded Phase 1 multiple ascending dose study ongoing (IM formulation)
- Process improvements, scale up, and tech transfer for both IM and IV formulations in progress
- FDA consultations planned re: animal rule approval pathway

Future Trajectory of the Ebola Therapeutics Program

- **Regulatory Pathway Elucidation**
  - A regulatory pathway remains unclear since the first therapeutic is being evaluated for efficacy in a clinical trail – uncertain if this will be achieved
  - Additional nonclinical work will likely be needed to support FDA approval of products under the Animal Rule

- **Manufacturing Process Improvement**
  - New manufacturing technologies need to be explored. Plant based technologies have proven a costly and time consuming approach to MCM manufacturing

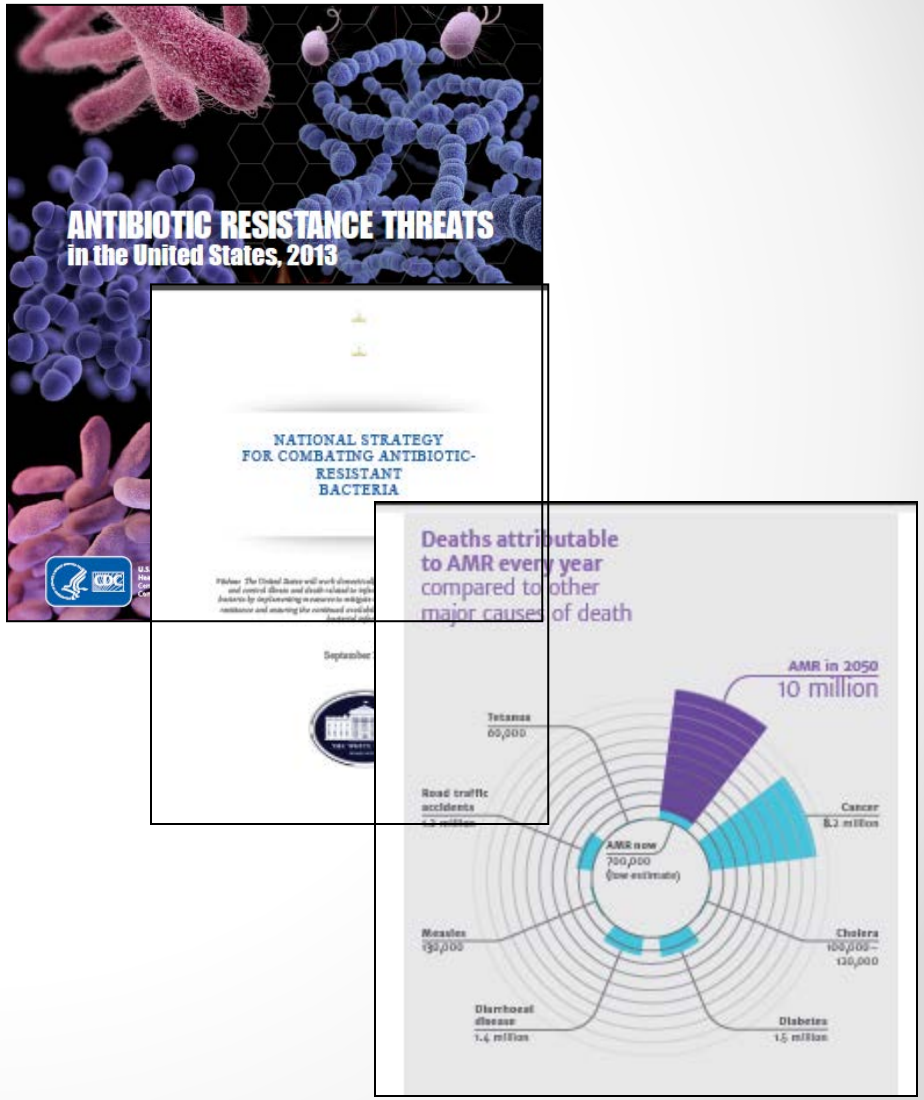
- **Fulfill Stockpiling Requirement**

Antibacterial Program Objective

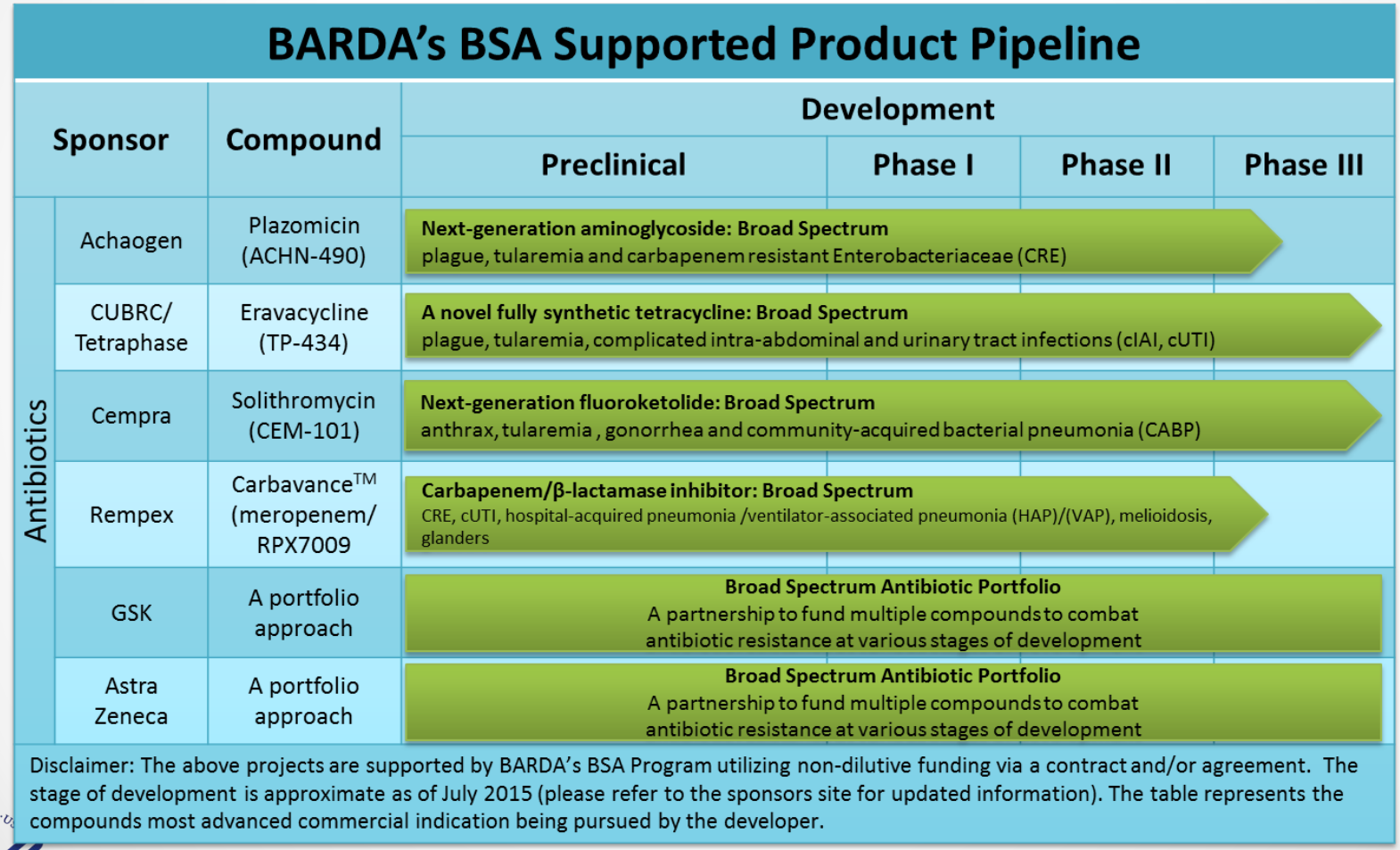
To help revitalize the antimicrobial pipeline by forming innovative public-private partnerships with companies engaged in antimicrobial therapy development

Why is BARDA Funding Antibacterial Development?

- To enhance biodefense preparedness
- To address the rising rate of antimicrobial resistance globally
- The pace of antibacterial drug development is/will not keep pace with the rate of resistance development without incentives.



Antibacterial Portfolio



Key Features of the BARDA-AZ Partnership

- Award date: September 15, 2015
- $50M base; $170M total if all options awarded
- HHS's 2nd ever use of Other Transaction Authority
- Program support a portfolio of antibacterial candidates, the cornerstone of which is aztreonam-avibactam (ATM-AVI)
- Fulfills requirement in CARB National Action Plan that ASPR/BARDA create at least one additional portfolio partnership with a pharmaceutical or biotechnology company by March 2016 to accelerate development of new antibacterial drugs
- Establishes international collaboration between BARDA and the EU's Innovative Medicines Initiative (IMI)
  - Both entities will provide support for ATM-AVI pivotal trials

AstraZeneca

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

Funding Priorities

Drug Class

- **Unprecendented**
  - Novel Target
  - Novel Chemistry
- **Precedented**
  - Reduced AR
- **Nontraditional Therapies**
  - mAbs, phage
- **Infection prevention/interdiction**
  - Vaccines
  - Microbiome approach

Antibiotic Resistance

- *C. difficile*
- CRE
- *N. gonorrhea*
- *Acinetobacter*
- ESBLs
- VRE
- *Pseudomonas*
- MRSA
- *Strep pneumo*
- VRSA
- *Streptococcus*

Biothreat

- *B. pseudomallei*
- *B. mallei*
- *F. tularensis*
- *Y. pestis*
- *B. anthracis*

Future Trajectory

- Key Tenets
  a. Develop novel classes antimicrobial therapies with a focus on those with Gram negative activity
  b. Continue utilizing innovative public-private partnering mechanisms to stimulate therapeutic pipeline
  c. Work closely with other Govt agencies and private partners to establish and implement policies/practices to ensure pipeline is sustainable

Future Trajectory

- Near-Term Priorities & Strategic Goals (1 years)
  a. Maintain and expand portfolio of precedented and unprecedented classes of antimicrobial therapies
  b. NDA Submission

- Mid-Term Priorities & Strategic Goals (2-3 years)
  a. NDA approval of BARDA-funded products
  b. Expand focus to include approaches that can interdict/prevent infection upon entry into the health care setting
  c. Expand portfolio to include non-traditional therapies (mAbs, probiotics, host targets, etc.)

Interfacing with BARDA

- www.phe.gov
  - Program description, information, news, announcements
- www.medicalcountermeasures.gov
  - Portal to BARDA
  - Register, request a meeting
  - Tech Watch
- www.fedbizopps.gov
  - Official announcements and detailed information about all government contract solicitations. Open CBRN BAA:
  - BAA-13-100-SOL-00013

Technical POC for Research Area #2: Anti-Toxins and Ebola Therapeutics

Chia-Wei Tsai, Ph.D., AI Project Officer

Chiawei.tsai@hhs.gov

Technical POC for Research Area #3: Antimicrobial Drugs:

Melissa Stundick, Ph.D. Chief AI Program

melissa.stundick@hhs.gov 202-205-7479