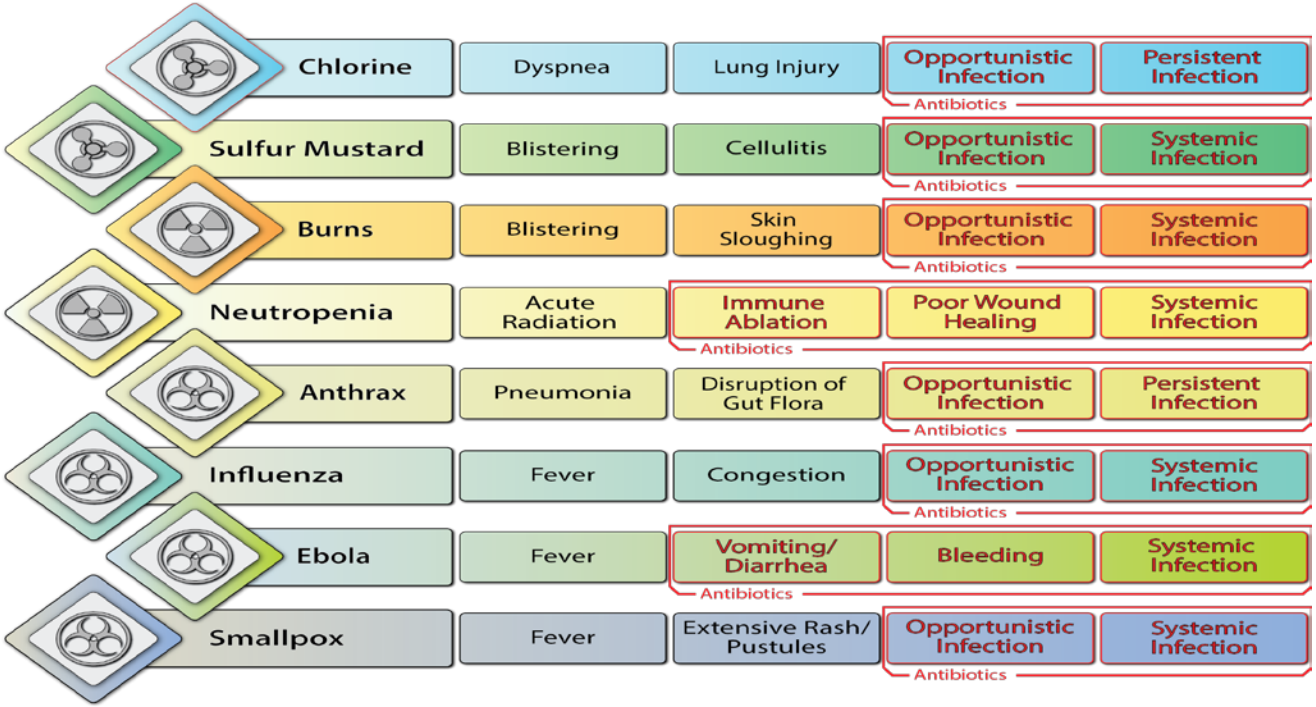
BARDA's CARB Progress Update

Joe Larsen, Ph.D.
Director
BARDA Division of CBRN Medical Countermeasures

PACCARB
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

CBRN Threats



BARDA Supported Push and Pull Incentives

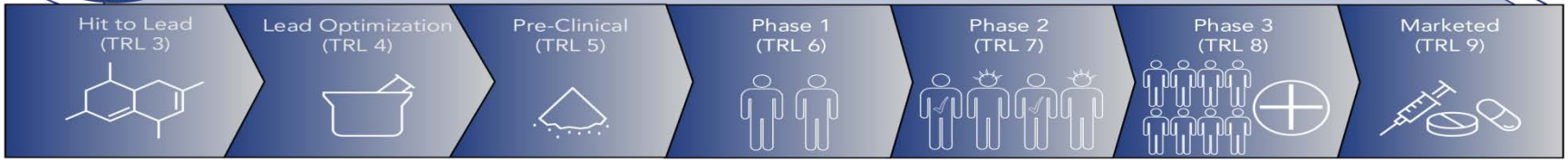
Pre-Clinical Development Pre-IND	Clinical Development Phase I-III	Marketing Post Approval
CARB-X	BARDA	CARBi
Push Inventive	***Push Inventive***	***Pull Inventive***
Direct Investment via Accelerators into Pre-Clinical Development	Clinical Stage Public Private Partnerships	A new model with Market Entry Reward & Stewardship
2016	***2010***	***TBD***

Holistic Set of Incentives to Promote Antibacterial Product Innovation

Note: Includes current and potential BARDA supported push and pull mechanisms. Other USG Agencies have complementary push and pull incentives that are not displayed on this page. CARB-X is co-funded with NIAID

What is BARDA doing to address Antibacterial Resistant Infections?

Investing $192 million in FY 2017 through Novel Public Private Partnerships to support a Portfolio of Antibacterial Products to repopulate the Antibacterial Pipeline



3 | 8 | 4 | 4 | 2 | 4 | 1

Total number of products supported

27

CARB-X

Updated August 9, 2017

Projections by SEPT 14

BARDA's Antibacterial Portfolio National Action Plan Metrics

BARDA Antibacterial Portfolio milestones from the 2015 National Action Plan for CARB	Status	Year Completed
ASPR/BARDA will create at least one additional portfolio partnership (Objective 4.6, Year 1)		2015
Two antibiotic drugs developed by portfolio partners for treatment of an urgent or serious pathogen (Table 1) will enter Phase III clinical investigation (Objective 4.6, Year 3)		2016 *(2 yrs. ahead of schedule)*
IND applications for at least two additional antibiotic drugs developed by portfolio partners will be submitted for FDA approval (Objective 4.6, Year 5)	On-Track	
U.S. agencies will also explore collaborations with the New Drugs 4 Bad Bugs (ND4BB) programs of the Innovative Medicines Initiative (Objective 5.5, Year 1)		2016

BARDA's Diagnostic Portfolio National Action Plan Metrics

BARDA's Diagnostic milestones from the 2015 National Action Plan for CARB	Status	Year Completed
BARDA) will fund at least three new diagnostic development projects that involve next-generation sequencing, multiplex molecular assays, or other new technologies that shorten the time needed for reliable and accurate detection of drug resistance (Objective 3.1, Year 3)		2017
NIH and ASPR/BARDA will establish a prize for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship (Objective 3.1, Year 3)		2016
At least one new diagnostic product, the development of which was facilitated by NIH or ASPR/ BARDA, will be submitted for FDA approval or clearance (Objective 3.1, Year 5)		2017
NIH and ASPR/BARDA will manage and administer a prize contest (see above) for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship (Objective 3.1, Year 5)	On-Track	2020

BARDA's Accelerator [CARB-X] National Action Plan

BARDA's CARB Biopharmaceutical Accelerator milestones from the 2015 National Action Plan for CARB	Status	Year Completed
ASPR/BARDA and NIH will work with a consortium of industry partners to develop a strategy for establishing the CARB Biopharmaceutical Accelerator (Objective 4.7, Year 1)	✓	2015
The CARB Biopharmaceutical Accelerator will be operational, with technical services in place to facilitate toxicology studies, animal challenge studies, and other activities needed to accelerate drug development (Objective 4.7, Year 3)	✓	2016 *(2 yrs. ahead of schedule)*
NIH and ASPR/BARDA will implement a strategy for assisting research partners who are developing novel classes of antibacterial drugs in fulfilling the requirements of FDA IND applications (Objective 4.5, Year 1)	✓	2015
NIH and ASPR/BARDA will meet on a semi-annual basis with investigators who participate in the Antibiotic Resistance Biopharmaceutical Incubator to evaluate progress in providing technical resources for in vitro and in vivo screening of resistant pathogens of public health concern (Objective 4.5, Year 1)	✓	2017
NIH and ASPR/BARDA will identify at least twelve candidate products for preclinical development support and support three candidate products from preclinical development through IND submission (Objective 4.5, Year 3)	On-Track	
BARDA and NIH will assess progress in meeting Accelerators five-year goals: (Objective 4.7, Year 5)		
• Identifying at least five targets for novel therapeutics	✓	2017
• Generating in vivo data to validate at least three of these targets	On-Track	
• Generating at least three antibacterial drug candidates	On-Track	
• Transitioning at least two of these candidates from preclinical testing to submission of an FDA IND application to begin clinical trials	On-Track	

Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator

CARB-X

Xccelerating global antibacterial innovation

CARB-X Overview

In 2016 NIAID and BARDA successfully launched the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) called out in the U.S. 2015 *National Action Plan for Combating Antibiotic-Resistant Bacteria*

CARB-X is a $455M global antibacterial innovation initiative utilizing a unique public-private partnership model

- A financial commitment over 5 year up to $250M for BARDA, $155M for Wellcome Trust and $50M in-kind from NIAID for pre-clinical services

CARB-X brings together BARDA, NIAID, Wellcome Trust as funders and three life science accelerators to identify, select, and manage a portfolio of early stage antibacterial candidates

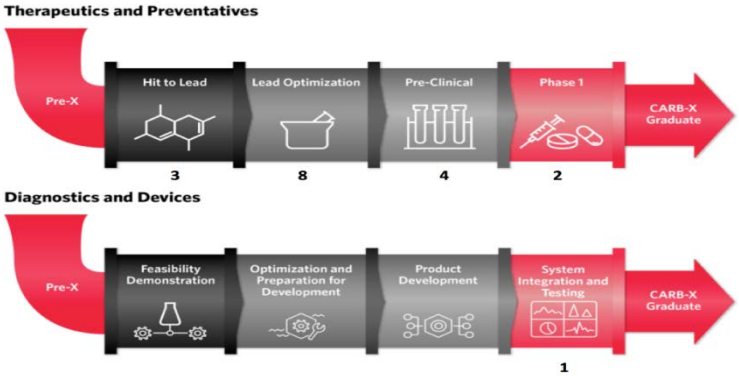
CARB-X will deliver novel antibacterial products to clinical development over the next 5 years and is on-track to address all National Action Plan metrics

A portfolio of ~20 antibacterial candidates

Private sector approach to funding/portfolio management

A minimum of 2 candidates progress to clinical development

CARB-X Accomplishments



- **Program operational 2 yrs. ahead of schedule**
- **A Global Innovation Fund leveraging a novel Public Private Partnership model with a 1 to 1 cost share**
- **CARB-X's Year #1 Accomplishments**
  - $41.6 million to support antibacterial pre-clinical development plus an additional $52.6 if project milestones are met
  - Targeting the most urgent drug-resistant Gram-negative bacteria, as prioritized by the WHO and CDC
  - 18 innovative projects funded, all potential game-changers in fight against drug-resistant bacteria. More projects to come in late 2017
  - 8 new classes of antibiotics in the pipeline
  - 368 applications received from researchers around the world
  - Providing fully non-dilutive funding, with wrap around business support services from world leading life-science accelerators
  - Global reach expanding with funded projects in 6 different countries and no geographic restrictions on funding

CARB-X

powered by

And currently seeking additional Funders

CARB-X Portfolio

Powered by CARB-X

The CARB-X portfolio comprises 18 early stage R&D projects investigating 8 new classes of antibiotics, 5 non-traditional antibiotics, 10 new molecular targets and a rapid diagnostic to determine the type of drug-resistant bacteria that is causing an infection.

Company/ Research Team	Project	Novelty*			Project description	Urgency/ Priority**	Bacteria Targeted / Stage of Early Development			
		New Class	Non-traditional	New Target			Hit to Lead	Lead Optimization	Pre-Clinical	Phase 1
Achaogen	AKAO-LpxC	✓		✓	LpxC Inhibitor	✓	*Pseudomonas aeruginosa*			
Antabio	PEI		✓	✓	Pseudomonas Elastase inhibitor	✓	*Pseudomonas aeruginosa*			
Bugworks Research	Gyrox	✓			Gyrase-topoisomerase inhibitor	✓	Gram-negative activity			
Cidara Therapeutics	CD201		✓	✓	Bifunctional immunotherapy	✓	Acinetobacter + *P. aeruginosa* + Enterobacteriaceae			
ContraFect	Gram-negative lysins		✓	✓	Recombinant lysin protein	✓	*P. aeruginosa*			
Debiopharm	Debio 1453	✓		✓	Narrow-spectrum inhibitors of FabI	✓	*Neisseria Gonorrhoeae*			
Eligochem	Helical AMP	✓			Helical Antimicrobial Peptide	✓	Gram-negative activity			
Entasis Therapeutics	ETX000				Oral Gram-negative combination	✓	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✓		✓	LpxC Inhibitor	✓	Gram-negative activity			
Iterum	Sulopenem				Oral and IV penem	✓	Gram-negative activity			
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	*Pseudomonas aeruginosa*			
Oppilotech	LPS	✓		✓	Targets synthesis of LPS	✓	Gram-negative activity			
Redx Pharma	NBTI	✓			Dual-acting topoisomerase inhibitor	✓	Acin. + *P. aerug* + Enterobacteriaceae			
Spero Therapeutics	SPR741			✓	Potentiator	✓	Gram-negative activity			
Tetraphase Pharm	TP-6076				Next-generation tetracycline	✓	Acinetobacter + Enterobacteriaceae			
VenatoRx	VNRX-PBP	✓			ß-lactamase Resistant PBP Inhibitor	✓	Entero-bacteriaceae			
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	*Pseudomonas aeruginosa*			

Company/ Research Team	Project	Project description	Development Stage			
			Feasability Demonstration	Optimization and Preparation for Development	Product Development	System Integration and Testing
Proteus	Rapid POC Diagnostic	Optical bacterial imaging	POC Diagnostic			

* Novelty characterizations of new class and new target are established by CARB-X following the Pew Trusts pipeline analysis model. Pew defines a novel chemical class as a group of antibiotics that share a new common core molecular structure. Non-traditional products include lysins and monoclonal antibodies.

** Urgent and priority drug-resistant bacteria are determined by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).
✓ Urgent/Critical priority ✓ Serious/High priority ✓ Serious/Medium priority.
Stage of development is approximate as of July 2017.

Powered by CARB-X

8 new classes of antibiotics

5 Non Traditional Approaches

10 New Targets

BARDA's Antibacterial (AB) Program Highlights

BARDA Highlights 2016-2017

VABOMERE

The Medicines Company

- August 2017, Rempex Pharmaceuticals received FDA approval for Vabomere to treat complicated urinary tract infections

- This is the first BARDA-supported antibiotic to be FDA approved.

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

BARDA Highlights 2016-2017

ACHAOGEN

- Achaogen completed all human clinical studies and plans to submit to the FDA their application to market Plazomicin to treat complicated urinary tract infections and infections due to drug-resistant bacteria.
- Achieved primary endpoints for cUTI
- Descriptive study in CRE infections showed lower rates of mortality or disease related complications compared with colistin therapy
- New Drug Application submission projected for late 2017

BARDA Highlights 2016-2017

TETRAPHASE PHARMACEUTICALS

- In July 2017, CUBRC/Tetraphase announced positive top-line results from a second registrational Phase 3 clinical trial evaluating the efficacy and safety of intravenous eravacycline for the treatment of patients with complicated intra-abdominal infections.

- New Drug Application submission is projected for 4QCY2017

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

BARDA Highlights 2016-2017

New Programs in FY2017

- BARDA is anticipating initiating a program for the development of an orally-administered beta-lactam/beta-lactamase inhibitor combo ***Goal: oral treatment of ESBL E. coli or Klebsiella pneumoniae infections***

- BARDA is anticipating initiating a program for the late stage clinical development of a *C. difficile* therapy.
  Goal: novel first in class treatment

BARDA's Phase I-III Clinical Investments

Barda's Antibacterial Timeline

Sponsor	Compound	Development Stage			
		Preclinical	Phase I	Phase II	Phase III
Achaogen	Plazomicin	**Next-Generation Aminoglycoside** cUTI/AP, CRE, Plague, Tularemia			
Rempex	Carbavance	**BI/BLI Combination** CRE, cUTI			
Cempra	Solithromycin	**Next-Generation Fluoroketolide** CABP, GC, Anthrax, Tularemia			
CUBRC/Tetraphase	Eravacycline	**Fully Synthetic Tetracycline** cIAI, cUTI, MDR			
Basilea	Ceftobiprole	**Cephalosporin** ABSSSI, SAB, CABP, Plague, Tularemia			
Astra Zeneca	Aztreonam-Avibactam	**BL/BLI Combination** cIAI, HAP/VAP, cUTI, BSI, MDR gram-, Melioidosis, Glanders, Plague			
GlaxoSmithKline	Gepotidacin	**Topo II Inhibitor** CABP, GC, uUTI, Plague, Tularemia, Anthrax			
GlaxoSmithKline	GSK-830	**Cephem BL** cUTI, cIAI, HABP/VAPB, MDR			
GlaxoSmithKline	GSK-680	**Topo II Inhibitor** TBD			
The Medicines Company	Carbavance	**BL/BLI Combination** HABP/VABP, MDR			
Hoffman-La Roche	RG6080	**Broad Spectrum BL** cUTI, cIAI, HABP/VABP, MDR			
CARB-X	Pre-Clinical Accelerator	**Hit-to-Lead to Phase 1**			

Where will BARDA Invest Going Forward

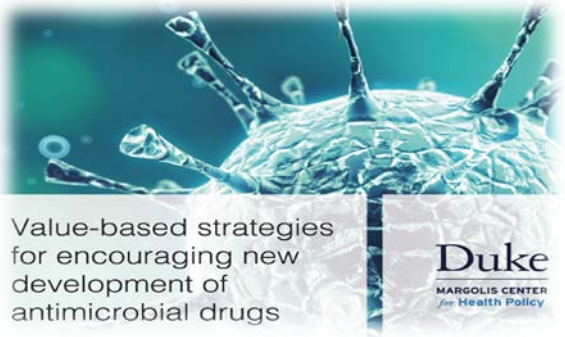
Pre-Clinical Development Pre-IND	*Clinical Development Phase I-III*	*Marketing Post Approval*
CARB-X	BARDA	CARBi
Push Inventive	***Push Inventive***	***Pull Inventive***
Direct Investment via Accelerators into Pre-Clinical Development	Clinical Stage Public Private Partnerships	A new model with market entry Reward & Stewardship
FY18-19 Investment Priorities		
Expand the CARB-X Portfolio and hit metrics	Diversify the portfolio & advance late stage products to Market	Engage Stakeholders to identify structure for Pull Incentives

Market Entry Rewards is the Missing Link to a Holistic Response

Note: Includes current and potential BARDA supported push and pull mechanisms. Other USG Agencies have complementary push and pull incentives that are not displayed on this page. CARB-X is co-funded with NIAID

Market Entry Rewards are Needed to Establish a Pull Incentive

- Antibiotics are one of the only class of drugs whose use diminishes utility overtime
- How do we ensure antibiotics are available while not driving inappropriate use?
- Market Entry Rewards models seek to uncouple profit of antibiotics from the number of units sold
  - Allow a reasonable return on investment (ROI)
  - Can build in provisions for stewardship and conservation

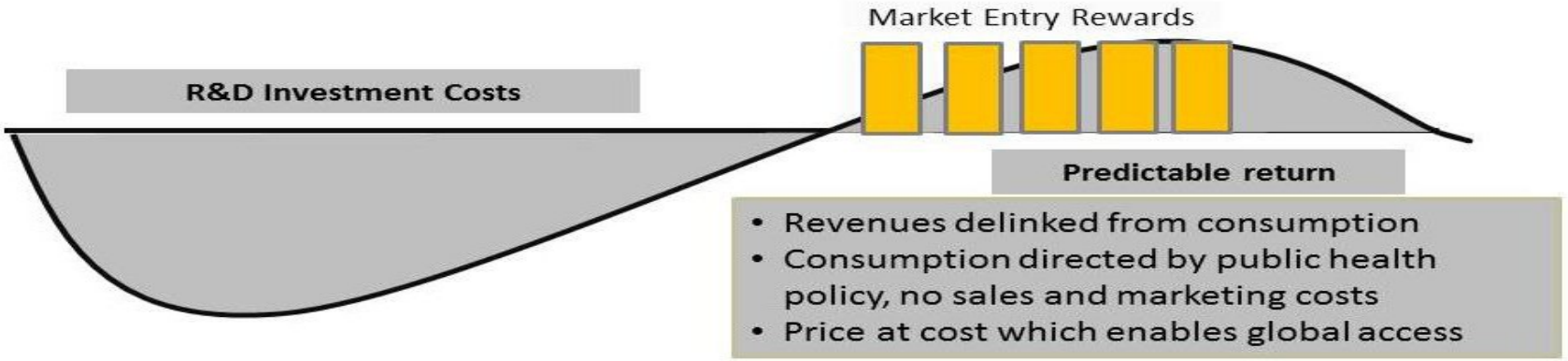


August 2016

September 2017

There is consensus in the community that a Pull Incentive is needed

Market Entry Rewards



BARDA has the track record and is strategically positioned to implement CARB Pull Incentives

- Supported FDA approval of 32 products since 2006
  - Project BioShield (15 Products Stockpiled and 7 Approved)

Summary

- BARDA continues to deliver on the goals set forth in the CARB National Strategy/Action Plan
- BARDA supported program led to the FDA approval of Vabomere, a new antibiotic to treat Gram-negative infections
- CARB-X is promoting innovation in antibacterial product development
- New market models, such as market entry rewards could be utilized to reward innovation while achieving public health objectives

Thank you

joseph.larsen@hhs.gov
202-260-0050