NIH's Role in Combating Antibacterial Resistance (CARB)

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Division of Microbiology and Infectious Diseases
NIAID, NIH, HHS

September 29, 2015
CARB Presidential Advisory Council

CARB Goal 4

Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines.

Objectives:

- 4.1.2: Leverage existing partnerships, such as the NIH ARLG, and international collaborations to reduce obstacles faced by pharmaceutical companies…
- 4.3: Intensify R&D of new therapeutics and new and improved vaccines…
- 4.4: Develop non-traditional therapeutics, vaccines, and innovative strategies…

NIAID Antibacterial Resistance Program

- Basic Research
- Translational Research/ Product Development
- Clinical Research

Diagnosis, Prevention and Treatment

Context: Antibacterial Development at NIAID

- Targeted funding opportunities:
  - 18 AR therapeutics-focused since 2010 (basic, translational and clinical research)
- Workshops
  - Development of New Antibacterial Products (with FDA; 2014)
  - Staph vaccines (2010 & 2013)
  - Bottlenecks in Drug Development (2012 & 2014)
- Extensive Infrastructure

DMID Resources for Researchers

Resources for Researchers

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Microbiology and Infectious Diseases Resources

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV.

Funding Opportunities

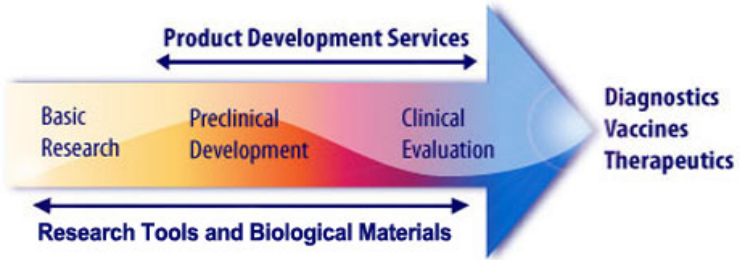
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- NIH-Wide Funding Opportunity Announcements
- NIAID Funding Opportunity Announcements and Requests for Proposals

Product Development Services and Research Tools and Biological Materials

Request development by DMID-funded contractors of critical information needed to move a product through the product development pathway. Note: Services are contingent upon availability of required preliminary data.

Click on labels below to view information on services.



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dmidresources@niaid.nih.gov

Highlight

Sharing Scientific Success Stories: DMID WOWS

Additional Information From NIAID

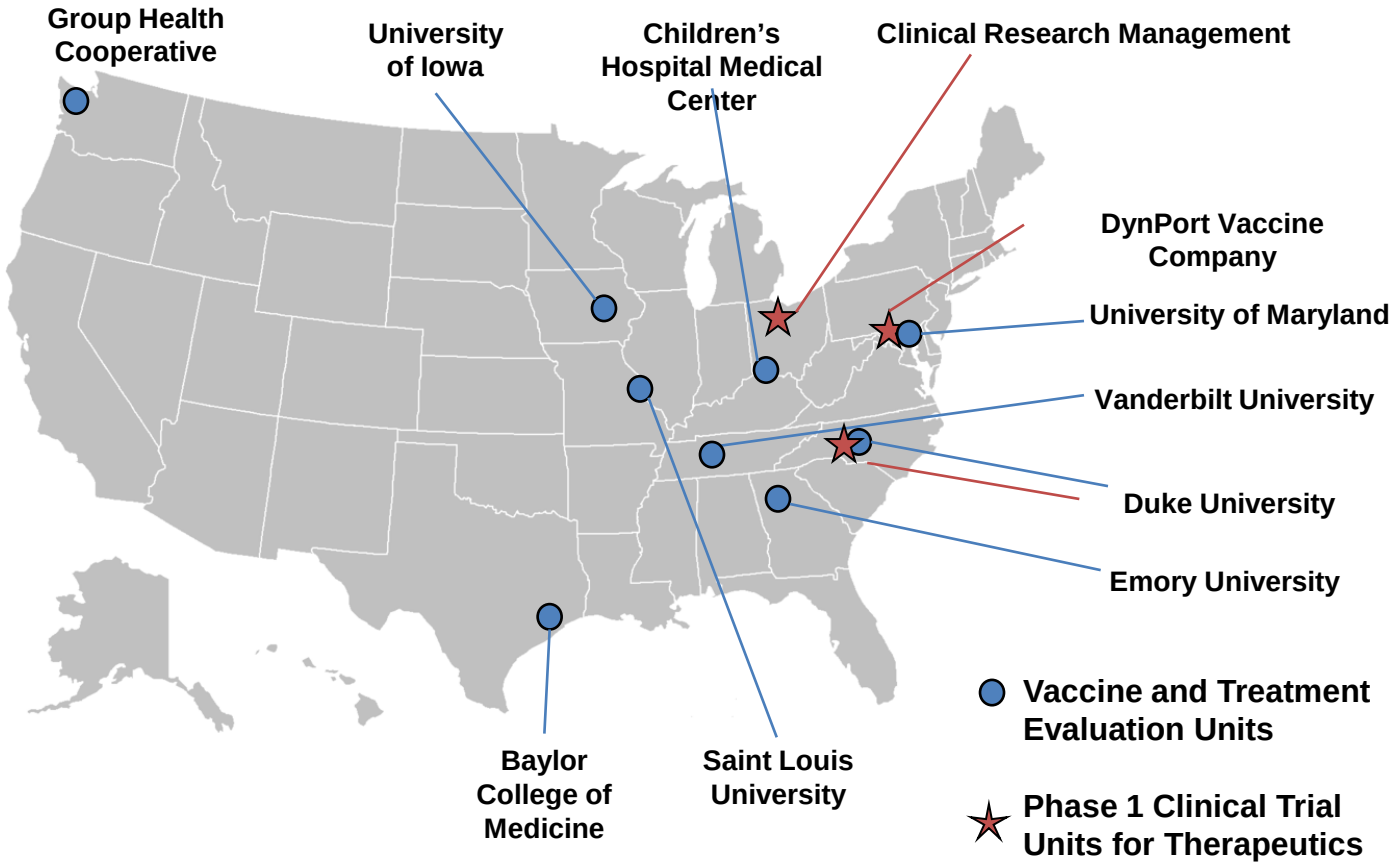
All NIAID resources

Web Search Term: **DMID Resources**

NIAID Preclinical Services

- *In vitro* Assessment for Antimicrobial Activity
- Animal Models of Infectious Diseases
- Therapeutic Development Services
  - Lead identification and development
  - Chemistry and manufacturing
  - *In vitro* microbiological services
  - *In vitro* and *in vivo* preclinical safety, toxicology and pharmokinetics
  - Preclinical development, planning and evaluation

Clinical Trial Units



ARLG
Antibacterial Resistance Leadership Group

The Antibacterial Resistance Leadership Group

Mission: To prioritize, design, and execute clinical studies that will reduce the public health threat of antibacterial resistance.

ARLG.org

Recent NIH CARB Activities – Objective 4.3

- RFA-AI-14-064: Systems Biology and Antibacterial Resistance.
  - Multi-disciplinary systems biology approach to study the molecular interaction networks of the pathogen and the host in the context of AR.

- Tetraphase Pharmaceuticals filed an IND for a novel tetracycline, TP-271, which is being developed with NIAID support. Phase I trial is planned.

- Recently funded 4 contracts under BAA-NIAID-DMID-NIH-AI-2014007, Targeting Therapeutics Development to Relieve Bottlenecks.

Recent NIH CARB Activities – Objective 4.4

Develop non-traditional therapeutics, vaccines, ...

- RFAs issued for non-traditional therapeutics and host-targeted therapeutics
- Workshops on bacteriophage therapy and the role of the microbiota in infectious disease; GC vaccine development
- Preclinical services support for Staph and Shigella vaccine candidates and defined product for Fecal Microbiota Transplant clinical trials

Future Directions

Objective 4.1.2: Leverage existing partnerships, such as the NIH ARLG, and international collaborations to reduce obstacles faced by pharmaceutical companies that are developing new antibiotics:

- Partnerships;
  - Companies, countries, other networks
- Populations;
  - Capturing sporadic and widely distributed infections
- Protocols
  - Enhancing efficiency and feasibility of trials
  - Working with FDA, ARLG and others to reach the goal line

Thank you

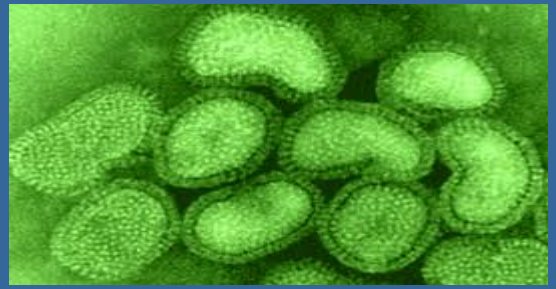
…for your interest

BARDA's Role in Combating Antimicrobial Resistance

Joe Larsen, Ph.D.
Deputy Director
BARDA Division of CBRN Medical Countermeasures
October, 2015

PRESIDENTIAL ADVISORY COUNCIL ON
COMBATING ANTIBIOTIC-RESISTANT BACTERIA

The BARDA Model



- The BARDA model works to address market failures
  - 21 Products FDA approved/cleared for biothreats and pandemic influenza
  - 13 Products stockpiled for emergency use
- This model is being successfully applied to antimicrobial resistance
  - Utilization of novel public:private partnerships to incentivize antibiotic research and development
  - 4 products in Phase III clinical development

BARDA's Antimicrobial Portfolio

BARDA's BSA Supported Product Pipeline

	Sponsor	Compound	Development			
			Preclinical	Phase I	Phase II	Phase III
Antibiotics	Achaogen	Plazomicin (ACHN-490)	**Next-generation aminoglycoside: Broad Spectrum** plague, tularemia and carbapenem resistant Enterobacteriaceae (CRE)			
	CUBRC/ Tetraphase	Eravacycline (TP-434)	**A novel fully synthetic tetracycline: Broad Spectrum** plague, tularemia, complicated intra-abdominal and urinary tract infections (cIAI, cUTI)			
	Cempra	Solithromycin (CEM-101)	**Next-generation fluoroketolide: Broad Spectrum** anthrax, tularemia , gonorrhea and community-acquired bacterial pneumonia (CABP)			
	Rempex	Carbavance™ (meropenem/ RPX7009	**Carbapenem/β-lactamase inhibitor: Broad Spectrum** CRE, cUTI, hospital-acquired pneumonia /ventilator-associated pneumonia (HAP)/(VAP), melioidosis, glanders			
	GSK	A portfolio approach	**Broad Spectrum Antibiotic Portfolio** A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development			
	Astra Zeneca	A portfolio approach	**Broad Spectrum Antibiotic Portfolio** A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development			

Disclaimer: The above projects are supported by BARDA's BSA Program utilizing non-dilutive funding via a contract and/or agreement. The stage of development is approximate as of July 2015 (please refer to the sponsors site for updated information). The table represents the compounds most advanced commercial indication being pursued by the developer.

Compliant Version is on page 47

Action Plan Metrics

- Within one year:

BARDA will create at least one additional portfolio partnership with a pharmaceutical or biotechnology company to accelerate development of antibacterial drugs.

BARDA and NIH will work to develop a strategy for establishing the Antibiotic Resistance Biopharmaceutical Incubator (ARBI).

Economic WG will provide an analysis of economic incentives and provide recommendations for implementation

Status

Program Initiated

Plan developed, no funding to initiate program

Recommendations provided to OSTP in March 2015

Key Features of the AZ Partnership

- HHS's 2nd ever use of Other Transaction Authority
- Partnership will support a portfolio of antibacterial candidates, the lead of which is aztreonam-avibactam (ATM-AVI)
- Strategic decisions will be made by a BARDA-AZ Joint Oversight Committee
- Establishes international collaboration between BARDA and the EU's Innovative Medicines Initiative (IMI)
  - Both entities will provide support for ATM-AVI pivotal trials

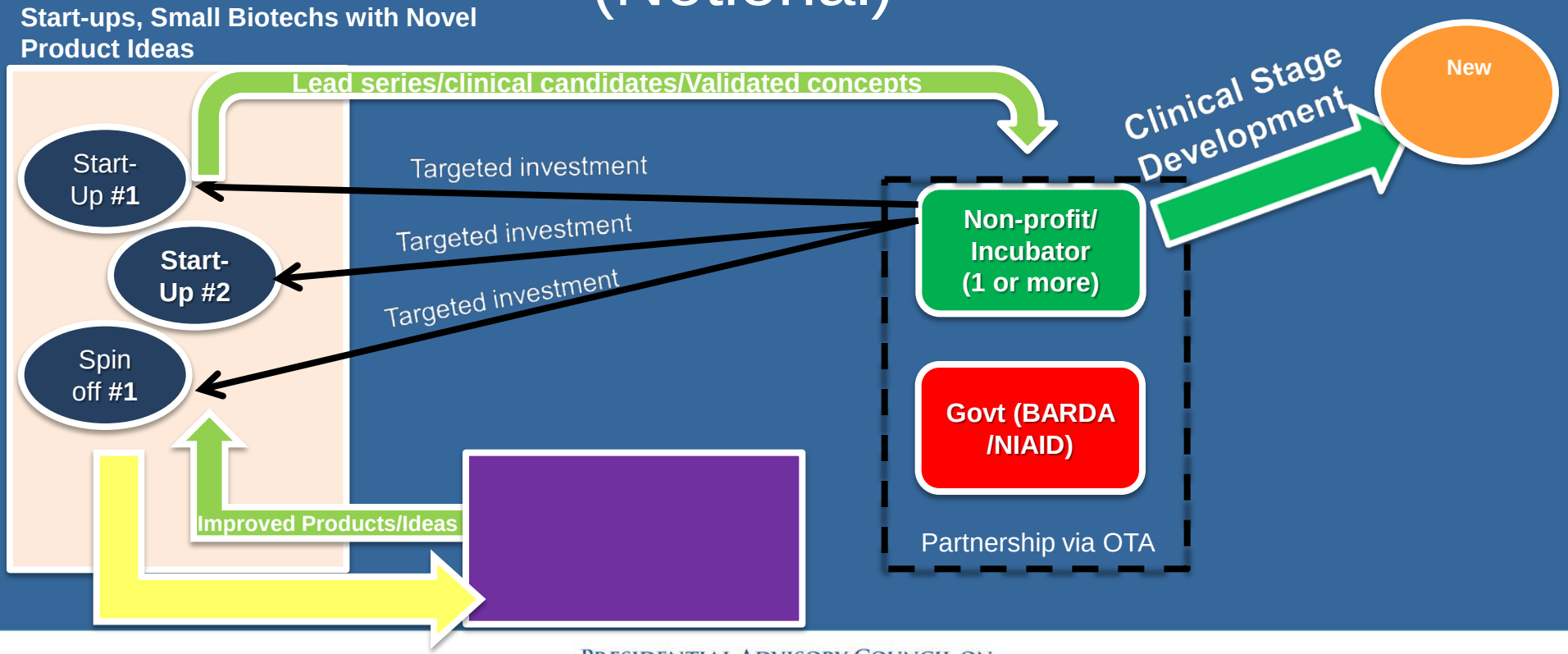
Incubator

- A robust early stage R&D pipeline of antimicrobial products is needed to counter the increasing threat of antimicrobial resistant infections
  - There is a need to create an environment to rapidly develop and commercialize new antimicrobial products

- NIAID and BARDA will collaborate to establish a new program using other transactional authority (OTA) to fund a Biopharmaceutical Incubator(s) to identify, assemble, and accelerate a portfolio of innovative early antibacterial products

- BARDA/NIAID have been conducting market research and have identified models that currently exist to support the Incubator concept

Proposed Incubator Process (Notional)

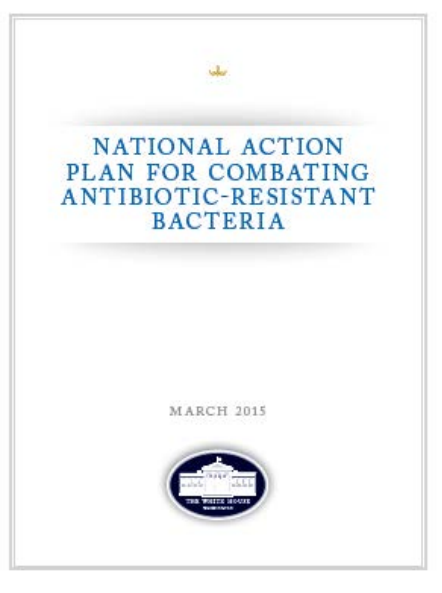


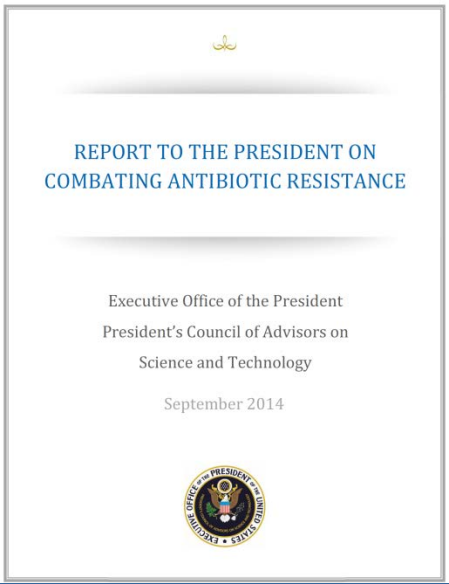
Incubator Models

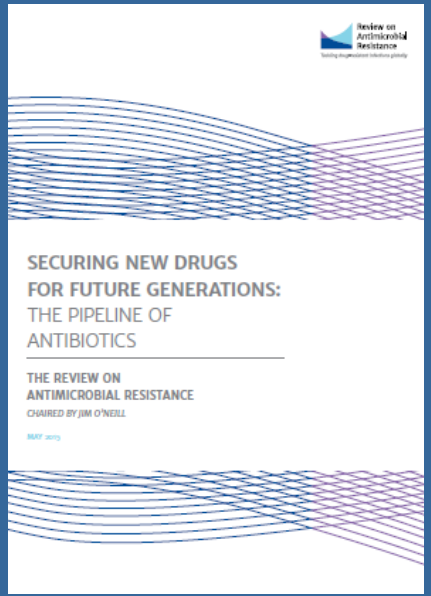
Any of the following models could support the Incubator concept:

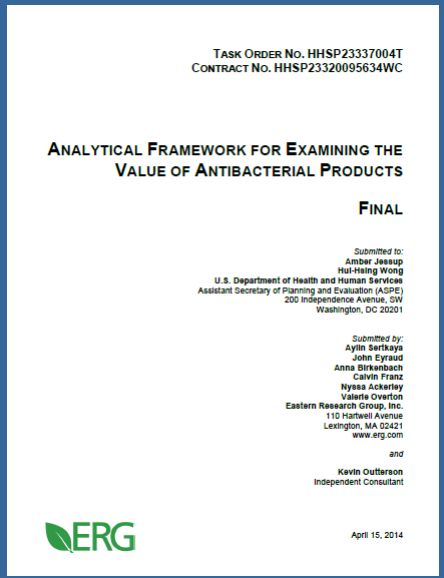
- Evergreen Life Science Funds
  - Leverage existing experience and funding streams
- State-run Incubators
  - States have tax credits and direct funding that the Incubator could leverage
- Non-profits
  - Could leverage and share resources to maximize Incubator's scope/impact

Economic Incentives









DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

CARB and Product Development

- BARDA has requested additional funding in FY16 to form additional public: private partnerships for antibacterial drug development

- It is unclear whether the proposed increase in push incentives will be sufficient to incentivize industry to remain committed to antibacterial drug development
  - 2014 CARB PCAST report suggests more incentives are needed

Summary

- BARDA's antimicrobial program will continue to support the development of novel antimicrobials and diagnostics to address the growing public health threat of antimicrobial resistance and biothreat pathogens

- Additional funding is required to accomplish most of BARDA's goals in the National Action Plan

- BARDA is actively conducting outreach to relevant stakeholders to communicate our plans to implement the CARB National Strategy

Interfacing with BARDA

- www.phe.gov
  - Program description, information, news, announcements
- www.medicalcountermeasures.gov
  - Portal to BARDA
  - Register, request a meeting
  - Tech Watch
  - BAA-13-100-SOL-00013

Technical POC for Research Area #3: Antimicrobial Drugs:
Melissa Stundick, Ph.D. Chief BSA Program
melissa.stundick@hhs.gov 202-205-7479

USDA Inputs for Goal 4: Research

Steven Kappes, PhD
Deputy Administrator
Animal Production and Protection
Office of National Programs
Agricultural Research Service
US Department of Agriculture

PRESIDENTIAL ADVISORY COUNCIL ON
COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Objective 4.1

Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans.

Objective 4.1

Within one year:

- **FDA, USDA, CDC, and NIH will host a roundtable of private and public sector experts to gather input on strategies to advance collaborative research to develop tools to combat antibiotic resistance using systems biology and other new technologies.**
- **FDA, USDA, CDC, and NIH will bring together experts in food production, agriculture, and public health to encourage collaborative research—from basic research to clinical testing—on antibiotic resistance.**

Objective 4.2

Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.

Objective 4.2

- No one year milestones
- Current activities:
  - USDA is funding/conducting studies on ecology and animal health

Objective 4.4

Develop non-traditional therapeutics, vaccines, and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.

Objective 4.4

Within one year:

USDA, with NIH, FDA, Ag industry, will develop a research and development strategy to promote understanding of antibiotic resistance and the creation of alternatives or improved use of antibiotics in animals.

Objective 4.4

Within one year:

USDA will solicit proposals that comprehensively develop research and outreach programs targeting development of novel alternatives to antibiotics for use in animals.

For Consideration

- It would be useful to develop a common set of definitions for terms and phrases such as multi-drug resistant, stewardship, and metrics for successfully reducing antimicrobial resistance to facilitate discussions.
- Given limited resources, what are the most urgent questions or possible solutions that should be addressed with research in developing alternatives to antibiotics?
- What are the obstacles to education/outreach and what are some possible solutions?

Thank You

Resources:

- **USDA AMR Action Plan: http://www.usda.gov/documents/usda-antimicrobial-resistance-action-plan.pdf**
- **NIFA-Funded Antimicrobial Resistance Work: http://nifa.usda.gov/antimicrobial-resistance**

Goal 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines

Edward Cox, MD MPH
Director, Office of Antimicrobial Products OND/CDER/OMPT/FDA

Background

- FDA works to facilitate the development & evaluation of antibacterial drugs
- Provide information (product labeling) on uses for which drug has been shown safe and effective
  - e.g., dosing & administration, adverse reactions, drug interactions, description of clinical studies, others…
- This work continues into post-approval period – additional indications of use, safety, breakpoint revisions, efficacy

Fragile Antibacterial Drug Pipeline

- Scientifically challenging area of drug development
  - urgent need to initiate therapy in seriously ill patients
  - diagnostic uncertainty
  - pre-study or overlapping antibacterial drug therapy can obscure evaluation of efficacy of an investigational drug
- Economically challenging area of drug development

GAIN

- Qualified Infectious Disease Product (QIDP) designations
- QIDP refers to an antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections, …
- QIDPs – often designated early in development
  - receive fast track designation upon request, priority review, 5 years of additional exclusivity
  - 87 QIDP designations
  - 60 unique entities
  - 6 entities w/ QIDP designation approved to date
- In general, most drugs that enter phase 1 are not ultimately shown to be safe and effective

Pathways for Development

- Guidance documents describe recommended pathways for development
- Emphasis on feasible, scientifically sound ethical clinical trials to evaluate antibacterial drugs
- 11 guidance documents published/revised since 2012
- HABP/VABP, cIAI, cUTI, GC, CABP, ABS, ABECB, ABOM, TB, ABSSSI, Unmet Need

Focus on Unmet Need

- Guidance document on streamlined drug development pathways for drugs with the capacity to address areas of unmet need
- Acceptance of greater uncertainty or risk for drugs that treat a serious infection where there are few or no available treatment options
- Indication of use includes a statement that use should be in situations when alternatives agents not available

LPAD

- LPAD Pathway (IDSA)
  - Streamlined development pathway
  - Serious disease unmet need
  - Means to designate as an LPAD drug
  - Pre-review of promotional materials
- Accelerate availability in areas of unmet need & tools to inform

Advancing the Science of Clinical Trials

- FNIH – developing & evaluating endpoints
- CTTI – trial efficiency and design
- Brookings Council on Antibacterial Drug Development – over-arching issues in antibacterial drug development
- Curating the science supporting clinical trial design and endpoints is key both here in the U.S. and for harmonizing available approaches internationally

Challenges / Opportunities - 1

- Developing narrow spectrum drugs (e.g., active against only a single species)
  - Means to show efficacy not clear if pathogen occurs infrequently
    - Number of patients needed using usual statistical conventions for a rare pathogen exceeds what likely can be achieved in relevant time frames
  - Rapid diagnostics important, but probably can't solve clinical trial problem & could help guide clinical use of such a drug

Challenges / Opportunities - 2

- Clinical trial network for studying antibacterial drugs
  - Infrastructure
  - Expertise
  - Lab support
  - Common protocol
    - Can study more than one drug – share control arm
  - Utility for diagnostic test development

Challenges / Opportunities - 3

- Updating breakpoints / interpretive criteria
  - Current “paper label” based process inefficient
  - Improve efficiency to better inform therapeutic choices and infection control in a timely manner
  - Leverage work of standards development organizations
  - FDA retains its authority re: scientifically appropriate breakpoints
  - Remove breakpoints from product label
  - Utilize FDA website to identify recognized breakpoints

- Thank you

BARDA's BSA Supported Product Pipeline

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Basilea	BAL30072	A novel sutfactam: Broad Spectrum MDR Gram negative infections, meliodosis, glanders
Rempex	Carbavance™ (meropenem/ RPX7009)	carbapenem/IJ-lactamase inhibitor: Broad Spectrum CRE, cUTI, hospital-acquftd pneunonia/ventillltor-msociated pneumonia (HAP)/(VAP), meliodosis, glanders.
GSK	A portfolio approach	Broad Spectrum Antibiotic Portfolio A partnership to fund multiple compounds to combat antibiotic resistance various stages of development.