THE ROLE OF THE BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY (BARDA) IN PROMOTING INNOVATION IN ANTIBACTERIAL PRODUCT DEVELOPMENT

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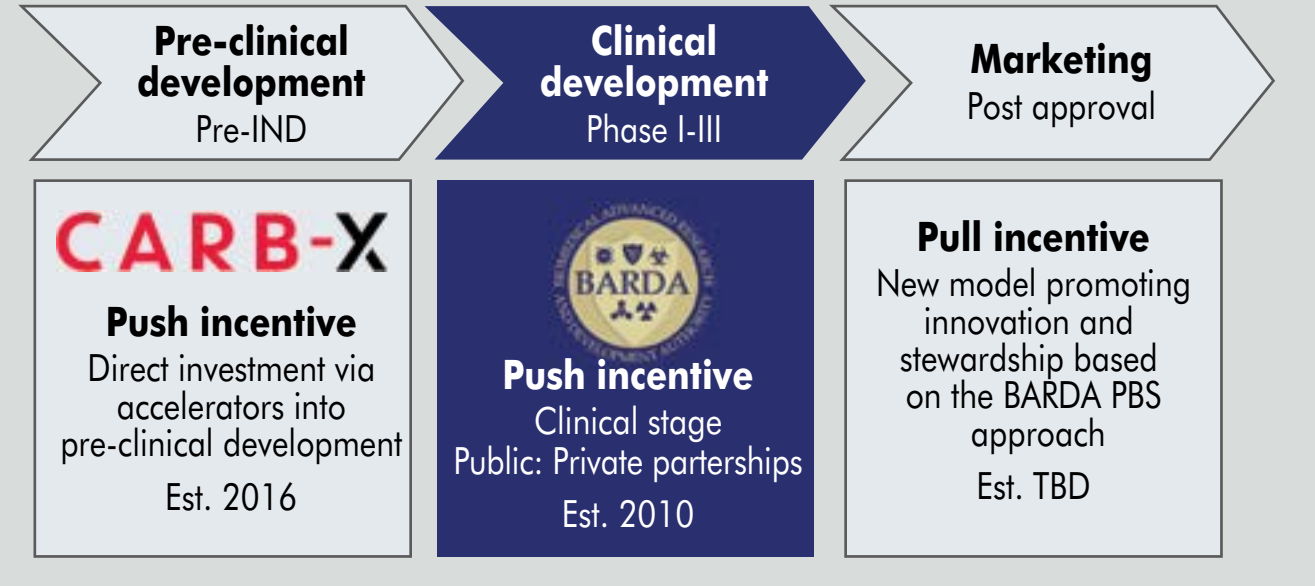
The Biomedical Advanced Research and Development Authority (BARDA) initiated a program in 2010 to address antimicrobial-resistant bacterial infections. Since then, BARDA has established several public-private partnerships aimed at the development of new antibacterial drugs and diagnostic platforms.

The Biomedical Advanced Research and Development Authority (BARDA) is a component of the United States Department of Health and Human Services tasked with preparing for and responding to mass public health emergencies. BARDA has an organizational remit to address chemical, biological, radiological, and nuclear (CBRN) threats, pandemic influenza and emerging infectious diseases. BARDA supports public-private partnerships with industry to develop medical countermeasures (vaccines, therapeutics, diagnostics) to respond to public health emergencies.

BARDA exists to address or correct market failures or challenges in public health emergency preparedness and response. An early example was the United States' lack of preparedness to effectively respond to a public health emergency that occurred during the anthrax attacks of 2001. At the time, there were very few companies developing medical countermeasures for bioterrorism agents and indications. To address the perceived market failure inhibiting the development of such countermeasures and to demonstrate the government's long-term commitment to biodefence, Congress passed the Project Bioshield Act which provided a ten-year US$ 5.6 billion fund for the procurement of medical countermeasures *(1)*. Subsequently, in 2006, to address the so-called "Valley of Death" characterizing late-stage development, United States Congress passed the Pandemic All Hazards Preparedness Act (PAHPA) which created BARDA and granted BARDA the authority to fund and provide other support for advanced research and development to de-risk medical countermeasure development programmes prior to procurement under Project Bioshield *(2)*. Together, these laws created an ecosystem of financial incentives significant enough to mobilize the pharmaceutical and biotechnology industry to pursue the research and development of medical countermeasures by overcoming the market challenges previously experienced. Since 2006, BARDA has supported the research and development of 25 products that have been approved and/or cleared by the FDA for use against biothreats and pandemic influenza, 15 of which have been stockpiled in the United States Strategic Stockpile for use in the event of a declared emergency.

Antibacterial drugs, vaccines and diagnostics play a critical role in protecting public health. BARDA recognizes the commercial and technical challenges associated with antibacterial drug development and determined that a set of financial incentives similar to those used to correct the biodefence medical countermeasure market could be applied

Figure 1: **BARDA's current and potential role in incentivizing antibacterial product development**



to antibacterial drug development. As a result, BARDA has formed multiple public-private partnerships that provide non-dilutive funding and technical advisory support to companies developing novel antibacterial drugs and diagnostics. The cornerstone of these partnerships is their flexibility and novelty. To date, BARDA's investments have supported six antibacterial candidates that have advanced to Phase III clinical development. Several new drug applications for BARDA-supported programmes are expected to be submitted to the United States Food and Drug Administration in the next one-three years. These outcomes will provide tangible measures of success by generating new options to treat drug-resistant bacterial infections. A depiction of BARDA's programmes and their means of incentivizing antibacterial product development is provided in Figure 1.

Current investments

BARDA's Broad Spectrum Antimicrobials Program was established in 2010 with the goal of establishing innovative public-private partnerships with companies engaged in antimicrobial therapy development to revitalize the antimicrobial pipeline. Currently, BARDA is partnered with nine companies supporting the development of 12 antibacterial candidates. These drug candidates target eight bacterial pathogens the CDC in 2013 identified as representing either urgent or serious threats to public health, including the so-called "nightmare" bacteria harbouring the mcr-1 gene that confers resistance against the "last-line of defence" antibiotic colistin. BARDA is partnered with small biotechs, such as Achaogen, Cempra and CUBRC/Tetraphae, mid-sized drug developers, including Basilea and The Medicines Company, and large, international pharmaceutical companies like Pfizer, GlaxoSmithKline and Hoffman-La Roche. Additionally, our industry partners are located both within and outside the United States. BARDA's funding decisions with respect to antibiotic development partnerships are driven by the quality of the supporting science and the alignment with public health priorities such as those outlined by the CDC in 2013.

BARDA's antibacterial portfolio is a very late stage portfolio of six programmes in Phase 3 development, with three of the six programmes having completed registrational clinical trials and two having filed NDAs. BARDA also has a very diverse portfolio of drugs with novel chemistries that overcome drug resistance mechanisms and have unique mechanisms of action classes, including novel aminglycosides and fluoroketolides, fully synthetic tetracyclines, beta-lactam/beta-lactamase inhibitor combinations, a first-in-class bacterial topoisomerase inhibitor, and a novel cephalosporin with broad-spectrum activity against both Gram-positive and Gram-negative bacterial pathogens. Additionally, each of our programmes, while addressing at least one public health threat identified by the CDC, is also supporting the evaluation of the drug candidate against a biothreat pathogen. While the BARDA portfolio is diverse in many aspects, it is comprised primarily of traditional small molecule antibiotics, though supporting the development of non-traditional approaches and technologies to address AMR is within BARDA's remit.

Innovative mechanisms of partnering

Portfolio partnerships

Many pharmaceutical companies have stopped developing new antibiotics due to a diminished return on investment

related, in part, to a high rate of candidate failure and attrition during development, limited and/or restricted patient use, and eventual product failure due to the emergence of drug resistance. Analyses have shown that for every 12 candidates entering Phase 1 clinical development, only one will receive FDA approval. For many pharmaceutical companies (and their investors), this is both technically challenging and financially daunting. Since 2013, BARDA has used an innovative and flexible contracting vehicle, called Other Transaction Authority (OTA), to establish public-private partnerships with large pharmaceutical companies (GlaxoSmithKline in 2013, AstraZeneca in 2015 (agreement was novated from AstraZeneca to Pfizer in 2017), The Medicines Company in 2016 and Hoffmann-La Roche in 2016) to reduce these barriers and incentivize antibiotic research and development. Other Transaction Agreements are designed to incentivize non-traditional government contractors to work with the federal government without having to modify their normal business practices. The use of OTA also allows BARDA to enter into international collaborations with other funding agencies to jointly support product development, as BARDA has done with the European Union's Innovative Medicines Initiative to co-fund the development of one of AstraZeneca's lead antibacterial candidates. Lastly, OTAs provide flexibility for the Government to enter into consortiums by accommodating the terms and conditions of licensing and collaboration agreements that a company may have in place with its partners, including provisions relating to the rights of licensors.

Importantly, public-private partnerships formed under OTA allow BARDA to take a "portfolio approach" to support a company's effort to simultaneously and in parallel develop multiple drug candidates. Such portfolio-based funding is also more consistent with industry practice and reduces technical risk by allowing for the reallocation of resources across activities and among drug candidates if technical or business risks materialize, thereby increasing the probability of bringing a successful drug to market. Through our current four OTA, we have supported the development of nine different antibacterial candidates in clinical development while also offering our industry partners future support for the development of promising candidates currently in their preclinical pipeline.

CARB-X

Currently, there is a substantial innovation gap in antibacterial drug development. A new class of antibiotics to treat Gram-negative hospital-acquired infections (HAIs), which often are more lethal and able to adapt to (and overcome) antibacterial drugs, has not been discovered in more than 45 years *(10)*. From 2007–2012, the total number of global patents filed for new antibiotics decreased 34.8% *(3)*. None of the antibiotics currently in the pipeline work through novel mechanisms of action. As a result, the current pipeline of new antibiotics addressing AMR is not robust and, based on historical rates of attrition, it is clear that the pipeline will not keep pace with increasing rates of antimicrobial resistance *(4)*. This partially reflects that innovation primarily occurs in small biotechnology companies and academic labs and such innovators often do not have the resources, expertise and/or know-how to move candidates along the development path from lead optimization to clinical development.

Recognizing this innovation gap, the United States National Strategy to Combat Antibiotic Resistant Bacteria was released in 2014 *(5)*. In it, BARDA and the National Institute of Allergy and Infectious Diseases (NIAID) were charged with establishing a biopharmaceutical incubator/accelerator to promote innovation in early-stage research and development of new antibacterial drugs, vaccines and diagnostics to repopulate the antibacterial pipeline. In response, BARDA launched the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, in July 2016.

CARB-X represents a global fund to promote innovation in antibacterial drug, vaccine, and diagnostic development *(6)*. CARB-X is a collaboration between NIAID and BARDA and three life science partners including the Wellcome Trust of London, the California Life Sciences Institute and MassBio. Boston University is the lead institution for CARB-X. BARDA is contributing up to US$ 250 million over the five years of the agreement, while the Wellcome Trust is providing up to US$ 155 million in additional funding to expand the scope and scale of CARB-X's impact. NIAID is providing access to preclinical resources for companies supported by CARB-X. The goal of CARB-X is to identify, select and manage a diverse portfolio of more than 20 high-quality antibacterial products towards first time in human testing within five years. CARB-X is designed to be scalable and will look to expand its scope and impact through the inclusion of additional accelerators as well as the formation of strategic partnerships with other government and non-government organizations interested in addressing antibiotic-resistant bacterial infections.

Diagnostics

Diagnostics are increasingly recognized as a critical component to address antimicrobial-resistant infections by facilitating the clinical evaluation and regulatory approval of candidate antibacterials and ensuring the appropriate use, stewardship and conservation of existing antibiotics. BARDA has supported a number of different partnerships and initiatives related to AMR diagnostic development. In September 2016, BARDA, in conjunction with the National Institutes of Health, announced a US$ 20 million prize for the

development of innovative laboratory diagnostic tools. Two primary sets of diagnostics tools are sought: those that can distinguish between viral and bacterial infections to reduce the unnecessary use of antibiotics and those that can identify and characterize antibiotic-resistant bacteria. The award of the prize in anticipated for late 2020.

BARDA is also supporting next generation sequencing technologies to rapidly detect pathogens in clinical specimens. BARDA is supporting DNAe's Genalysis® platform, which allows for the sequencing and identification of the organism in a sealed microchip-based system directly from a blood sample within a few hours.

Future directions

Over the past seven years, BARDA has established a robust portfolio of public-private partnerships that have infused non-dilutive funding in both the pre-clinical and clinical phases of antibiotic development. BARDA recognizes that addressing the challenge of AMR will require expansion of the therapeutic armamentarium beyond bacteriostatic and bactericidal small molecules. Areas of future investment will likely include greater emphasis of non-traditional approaches, such as monoclonal antibodies, microbiome modulation, phage therapy, etc. Vaccines for AMR pathogens will also be considered for BARDA support as a component of a longer-term sustainable strategy to combat AMR.

BARDA currently provides funding for companies to support research and development activities. This "push" incentive subsidizes research and development costs, thus increasing the return on investment for the candidate antibacterial drug. Several reviews have concluded that a constellation of economic incentives are needed to stimulate antibacterial drug development and promote innovation in this therapeutic area *(7, 8)*. A missing component is a strong pull incentive that would reward successful development of an antibacterial drug and would provide a known return on investment. Such a pull incentive could be structured to promote broader public health objectives such as stewardship and conservation. Economic models that de-link the profitability of an antibiotic from the volume sold are increasingly being promoted as a viable option to redefine the business model for new antibiotics to better align it with public health objectives *(9)*. BARDA's experience administering both push and pull incentives to create a viable marketplace for bioterrorism medical countermeasures positions us organizationally to be capable of administering such an incentive model for new antibacterial drugs. ■

Dr Chris Houchens, PhD, is the Branch Chief of BARDA's Antibacterial Program. He manages a diverse portfolio of novel therapeutics targeting the global threat of antimicrobial resistance, while also conducting outreach with academia and industry to identify new public-private partnership opportunities to strengthen BARDA's portfolio of antimicrobial products. Dr Houchens leads multiple interdisciplinary product development teams responsible for advancing the development, manufacture, clinical and non-clinical evaluation, and regulatory approval of novel drugs against multidrug-resistant organisms, emerging infectious diseases and biothreat agents.

Dr Joe Larsen, PhD, is Deputy Director of the Division of CBRN Medical Countermeasures within the Biomedical Advanced Research Development Authority (BARDA). In that role, he oversees a US$ 2.8 billion fund for the development and procurement of medical products for use during public health emergencies. He is also the BARDA lead for BARDA's work on combating antibiotic-resistant bacteria and has chaired intergovernmental working groups on research and development and economic incentives for antibacterial drug development.

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