

April 19, 2014

WHO White Paper on Innovative Models to Enhance Antibiotic Development

Description of BARDA/BSA program

The Biomedical Advanced Research and Development Authority (BARDA), part of the United States Department of Health and Human Services, seeks to enhance national preparedness for chemical, biological, radiological, and nuclear threats, pandemic influenza, and emerging infectious diseases by supporting innovation, developing and acquiring medical countermeasures, and building manufacturing infrastructure. BARDA's Broad Spectrum Antimicrobials (BSA) program was established in June 2010 with the goal of re-vitalizing the antimicrobial pipeline through the support of advanced research and development of novel antimicrobial drugs. BARDA recognizes that new antimicrobials are needed immediately to address the increasingly prevalent public health threat of antibiotic resistance, as it is likely to complicate standard treatment of a wide array of infections. At the same time, BARDA acknowledges that antimicrobial resistance can complicate the response to a public health emergency (natural disaster, flu outbreak, etc.). Through the establishment of innovative public-private partnerships, BARDA hopes to help revitalize the antimicrobial pipeline by providing incentives for pharmaceutical and biotechnology companies to engage (or reengage) in antimicrobial development.

By engaging with BARDA in a contract/agreement, our industry partners are able to receive funding and expert technical advice from BARDA for nonclinical studies, clinical studies (Phase 1-3), manufacturing, and regulatory activities. Unlike the interaction that typically occurs when researchers are supported by grants, BARDA engages its industry partners in a more comprehensive and holistic manner. BARDA provides technical support and guidance on all facets of drug development and works with its industry partners as true collaborators.

The BSA program's non-dilutive funding strategy provides our partners with capital to support product development and supplement existing equity. BARDA has successfully established public-private partnerships with industry partners to further the development of novel antimicrobials and anticipates a long-term commitment to this therapeutic area. BARDA has consistently seen the companies we partner with raise additional funding in private markets, become more attractive targets for purchase, enter into co-development arrangements and/or move forward with Initial Public Offerings (IPOs). While there are factors that impact each business decision our partners have made, it is clear that those that have partnered with BARDA have continued to achieve important technical and business milestones. Securing technical guidance and financial resources through a BARDA partnership is more frequently viewed by investors as a step to mitigate drug development risks. In addition, it frees up additional resources to help a company to grow and diversify. BARDA is seen by our partners, and their investors, as a collaborator that mitigates regulatory uncertainty as a result of our direct involvement with multiple antibiotic development programs. If antibiotics supported under a BARDA partnership are seen to advance more rapidly through drug development, and ultimately result in approved products, then BARDA's technical guidance could become as important as our non-dilutive funding.

In May 2013, BARDA further exemplified our ability, and commitment, to innovatively interact with companies when we entered into a strategic alliance with GlaxoSmithKline to launch a "Portfolio Partnership." Instead of focusing the program on a single antimicrobial candidate, an entire portfolio of candidate antimicrobial therapies is supported. This "Portfolio Partnership" is a 5 year \$200M agreement that utilizes a unique authority within the United States Government called Other Transactional Authority. This authority allows HHS to enter into an Other Transaction (OT) Agreement. An OT Agreement is essentially an agreement that is formed between the government and an industry partner (or partners) that is constructed *de novo*, free from many regulations present within Federal

April 19, 2014

Acquisition Regulations. The agreement with GSK possesses three central tenets: 1) flexible technical scope, 2) cost sharing, and 3) joint strategic oversight. The agreement is flexible as it allows for candidates to be incorporated, or removed, from the portfolio over the course of the agreement. It allows for the level of resources invested in each candidate product to be adjusted in real-time and the development plan for each candidate to be modified or revised, as needed. The agreement is governed by a Joint Oversight Committee (JOC) that consists of senior leadership from both GSK and BARDA. The JOC meets approximately every six months and makes all major decisions on the composition of the portfolio and the activities that are to be performed during the subsequent six month period. Overall progress on the agreement is monitored by BARDA's In-Process Reviews using federal interagency subject matter experts and leaders to deliberate and provide recommendations on overall BARDA funding for the agreement periodically. This type of long-term partnership sends a strong signal of commitment to industry, as the agreement is able to withstand the potential attrition of candidates that is commensurate with traditional pharmaceutical development.

Under the BARDA-funded programs, our partners are able to receive reimbursement for drug development activities in real-time. This is in contrast to a model where reimbursement is only provided after the purchase of product, as an advanced market commitment, or a milestone or prize payment upon advancing a candidate antimicrobial to a certain developmental point. The near real-time direct reimbursement for drug development activities is a preferred structure, as it shares the financial risk with the government. The non-diluted funding provided by BARDA to support development activities does not need to be repaid and does not dilute shareholder's equity. Further, the funding favorably impacts the net present value calculation of our partners by reducing their upfront costs. BARDA's support also does not require future royalty payments. The growth of the BSA program from one partnership in September 2010 to six antibacterial development partnerships today, with three of our partner's having antibiotics in Phase III, we believe validates our model.

Other Models Proposed by Industry and Academic Groups

Some experts have recommended advanced market commitments, where the government would commit, in advance, to purchase a prescribed number of novel antibiotics. This would be utilized particularly for antibiotics that would be reserved for very limited use against the most dire, untreatable infections. There is some concern over the long-term sustainability of this model. First, there is concern that the government would not be able to put up enough of an investment to actually change the economic model. The level of market share committed would need to be substantive enough to entice developers while considering financial principles like present value, specifically the need to "discount" a future guaranteed purchase to the present value. Estimates commonly provided suggest that a market commitment between \$250-500M per candidate product would be required. Such a commitment would represent a government investment of several billion dollars to ensure there was a sufficient market share for each company. If BARDA moved to this type of model, it would likely require a move away from our current funding strategies of reimbursement in real-time for drug development activities. Second, is the long term concern that the government would be creating a market where the major driver for profitability is directly proportional to the level of government subsidization. Third and most important, BARDA purchases of antibiotics for biothreats are tied to PHEMCE requirements and the level of preparedness that HHS senior leaders are able to accommodate amidst competing budget priorities and constraints. The quantities of antibiotics purchased by BARDA under Project BioShield may be less than that estimated by industry to make this approach feasible.

April 19, 2014

Antimicrobial stewardship will be critical as new drugs come to market. Various experts have proposed a need to move away from an economic model that is based on units sold as the driver of profitability. This would require a market adjustment where antimicrobial drugs that possess narrow label indications command much higher prices and target patients with the most dire, untreatable infections. The clear mortality benefit of antibiotics to treat multi-drug resistant (MDR) infections could be a major factor that could justify pricing reforms. Oncology therapies, which often command prices significantly higher than antibiotics, often only extend quality life years and are often not curative. Thus, therapies that provide a clear mortality benefit against untreatable infections should be priced similarly to oncology therapies. Barriers to this include whether payers will allow these pricing reforms to occur. Ultimately, it is unlikely that substantive market reforms will transpire until the prevalence of MDR infections reaches a level of greater crisis that necessitates immediate action.

Alternatively, other experts propose providing institutional licenses for antibiotic use/prescription as a means to ensure use in limited populations where the medical need is greatest. Tracking of antibiotic use could be a requirement of the licensing agreement and monitoring and enforcement of prudent use would be conducted by the company. This model would effectively remove units sold as the primary driver of profitability. However, the number of licenses sold would remain a constant force in commercialization of the product.

Overall, it is clear that multiple and coordinated incentives need to be established or sustained to bolster the pipeline of candidate antimicrobial therapies. Further, reforms to the commercial market are necessary to alter the commercialization path for new antimicrobial therapies particularly to account for preserving new antimicrobial therapies for the treatment of the direst resistant infections. Sustainability of any potential incentives needs to be a primary consideration.