AMENDMENT TO
BROAD AGENCY ANNOUNCEMENT FOR THE ADVANCED DEVELOPMENT OF MEDICAL COUNTERMEASURES FOR PANDEMIC INFLUENZA

Broad Agency Announcement Number: BAA-13-100-SOL-00019

Amendment Number: 0002

A. SUMMARY OF CHANGES

This Amendment (i) authorizes the use of Other Transaction agreements for all Areas of Interest in the BAA, (ii) extends the period of the BAA by one year, and (iii) issues two new subsections to Area of Interest No. 4, Influenza Therapeutics.

Except as provided herein, all other terms and conditions of the BAA remain unchanged.

B. AMENDMENTS TO BAA

(1) The section entitled Contractual Guidance in the Part entitled Guidance for Potential Offerors is changed by adding the following to the end of the second paragraph:

"The Government may elect to make Other Transaction (OT) agreements under this BAA."

(2) The section entitled Contractual Guidance in the Part entitled Guidance for Potential Offerors is changed by replacing the first sentence of the last paragraph with the following:

"This BAA is valid during the period from the date of issuance through **July 30, 2015**, unless announced otherwise."

(3) The section entitled Section 1: The Application Process in Part IV is changed by adding the following new Deadlines for Submission for *Stage 1: Quad Chart and White Paper* submissions:

Additional Deadlines for Submission
October 31, 2014 January 30, 2015 April 30, 2015 July 30, 2015

(4) The section entitled Area of Interest #4: Influenza Therapeutics in Part I is changed by adding the following Special Instructions after the last paragraph:

Special Instructions

1. ADVANCED DEVELOPMENT OF IMMUNOTHERAPEUTICS AND IMMUNOMODULATORS FOR THE TREATMENT OF INFLUENZA UNDER AREA OF INTEREST #4: INFLUENZA THERAPEUTICS

A. BACKGROUND

BARDA funds the advanced research and development of vaccines and therapeutics for which there is a critical unmet medical need. The priorities of the BARDA Influenza Division are closely aligned with the *National Strategy for Pandemic Influenza* (November 2005), the *National Strategy for Pandemic Influenza Implementation Plan* (May 2006), *The Public Health Emergency Medical Countermeasures Enterprise Review* (August 2010), the President's Council of Advisors on Science and Technology report on influenza vaccine manufacturing (August 2010), and the *BARDA Strategic Plan 2011-2016* (October 2011).

To achieve the goals described in these plans and to prepare the nation to be able to reduce significant morbidity and mortality caused by influenza, BARDA has focused its efforts on the advanced development of next-generation vaccines, antivirals, and diagnostics. The need for next-generation influenza therapeutics, such as anti-influenza monoclonal antibodies, is critical given the potential for rapid emergence and spread of viral resistance to adamantanes and neuraminidase inhibitors, the only antivirals currently approved in the US to treat influenza. Specifically, Goal 4 of the *BARDA Strategic Plan* calls for BARDA's next-generation influenza antiviral drug advanced development program to pursue new classes of drugs and innovative candidate antiviral therapies that will be less susceptible to viral resistance.

In addition to the critical need for new classes of antivirals and immunotherapeutics, the recent H1N1 pandemic highlighted the need for drugs that can be used later in the course of infection to treat severely ill, influenza infected patients who are hospitalized. Currently, there are no treatments approved for severely ill, hospitalized influenza patients. Many of these patients also suffer from secondary bacterial infections or increased sickness due to an overactive immune response. To make available effective treatments for this population BARDA will support the development of host-directed therapeutics, such as small molecule immune modulators, anti-inflammatory agents, and regulators of innate immunity that have been shown to be effective against influenza.

The BARDA Influenza Division is seeking proposals for Area of Interest 4: Influenza Therapeutics in which the candidate drugs are either:

1. Neutralizing monoclonal antibodies that broadly neutralize Influenza A, B or both A and B strains
2. Immunomodulators that a) improve the clinical response to and/or resolution of symptoms associated with influenza infection, or b) reduce the severity of the disease associated with an immune response to influenza infection.

B. SCOPE UNDER AREA OF INTEREST #4: INFLUENZA THERAPEUTICS

4.2 Neutralizing monoclonal Antibody Therapeutics for the Treatment of Influenza A, B or both A and B

BARDA seeks to develop neutralizing monoclonal antibody-based therapeutics for the treatment of influenza infection. For influenza A, monoclonal antibodies that are broadly neutralizing across Group 1 and Group 2 influenza A strains are most desirable, followed by antibodies that neutralize Group 1 or Group 2 influenza A strains individually. For influenza B, monoclonal antibodies that are broadly neutralizing across all strains is desired. A demonstrated ability to neutralize a broad spectrum of influenza subtypes and strains is highly desired. Monoclonal antibody cocktails that broadly neutralize both Influenza A and B strains would also be considered positively.

Demonstration of efficacy as measured by a significant reduction in morbidity, mortality or viral titers (for example) in relevant influenza infection animal models is required. Demonstration of safety and clinical benefit against influenza infection in human clinical studies is required. Antiviral activity against a spectrum of influenza subtypes and strains should have been demonstrated *in vitro* and *in vivo*. The strongest proposals will have data that demonstrates significant antiviral activity when given late in the course of disease (>48 hours after symptom onset) or that demonstrate improved efficacy when compared to neuraminidase inhibitors and in viruses resistant to current therapies. Consideration will also be given to proposed combination therapies of neutralizing monoclonal antibodies with approved influenza antivirals such as NAIs and adamantanes with demonstrated Phase 1 human safety and efficacy data.

The strongest proposals will have data on selection of escape mutants and mechanism(s) of resistance, providing a reasonable expectation that resistance development in the clinic will be slow, rare, or induce a strong fitness cost to the virus.

Evidence of supportive responses from the FDA concerning the development plan of the drug for influenza will reduce risk to a potential investment by BARDA and will support the strongest proposals.

Special populations:
Neutralizing monoclonal antibodies against influenza that offer therapeutic benefit to special populations, such as pediatrics and the elderly, will be favored. The strongest proposals will have specific plans to advance a product for approved use in special populations.

The strongest proposals will demonstrate more developmental maturity and therapeutic advantages when compared to the existing antiviral drugs. Formulations that favor ease of use and long shelf life are highly desired. Drug candidates must have an IND filed and completion of a Phase 1 clinical trial for evaluation of safety and effectiveness against influenza infection.

4.3 Immunomodulators

A. Immunomodulators that improve the clinical response to and/or resolution of symptoms associated with influenza infection

One approach to address the problem of antiviral resistance is to develop drugs that target the host, such as immunomodulators which can augment the immune system in a way that improves the host response to influenza infection and decreases the likelihood of viral escape mutants. BARDA seeks to develop immunomodulators that improve the response to influenza infections in people. Potential drug candidates such as small molecules, monoclonal antibodies, and other classes of drugs will be considered.

B. Immunomodulators that reduce the severity of the disease associated with an immune response to influenza infection

One hallmark feature of pandemic strains such as the 1918 pandemic strain and H5N1 is that they can have the ability to induce an exacerbated immune response (1). These strains have been shown to induce a higher level of pro-inflammatory immune cells and cytokines in the lungs than seasonal influenza viruses (2). BARDA seeks to develop immunomodulators that reduce the negative effects associated with the pro-inflammatory immune response induced following influenza infection. Potential drug candidates such as small molecules, monoclonal antibodies, and other classes of drugs will be considered.

For all immunomodulators, demonstration of the ability to safely modulate the immune system in an animal influenza virus infection model is required. Demonstration of efficacy as measured by a significant reduction in morbidity, mortality or viral titers (for example) in relevant influenza infection animal models is required. Demonstration of safety and clinical benefit against influenza infection in human clinical studies is required. The strongest proposals will provide comparative and/or synergistic safety and efficacy data in combination with neuraminidase inhibitors.

Evidence of supportive responses from the FDA concerning the development plan of the drug for influenza will reduce risk to a potential investment by BARDA and will support the strongest proposals.

Special populations:
Immunomodulator drugs that offer therapeutic benefit to special populations, which may include pediatrics and the elderly, will be favored. The strongest proposals will have specific plans to advance a product for approved use in special populations.

The strongest proposals will demonstrate more developmental maturity and therapeutic advantages when compared to or, in addition to, existing influenza antiviral drugs. Drug candidates must have an IND filed and completion of a Phase 1 clinical trial for evaluation of safety and effectiveness against influenza infection. Formulations that favor ease of use and long shelf life are highly desired. Drug candidates that are already approved for another indication will be considered if data from relevant influenza infection animal

models and human clinical trials supporting an influenza indication are included in the proposal.

C. PROPOSALS UNDER SPECIAL INSTRUCTIONS:

Offerors are required to follow the proposal submission guidelines in the BARDA BAA-13-100-SOL-0019. Quarterly deadlines for Quad Chart and White Paper submissions apply to these special instructions.

No individual pre-proposal conference will be held for these special instructions under BARDA BAA-13-100-SOL-0019. Information provided at the pre-proposal conference remains applicable for these special instructions.

The Government reserves the right to award the instrument best suited to the nature of the research proposed and may award any appropriate contract type under the Federal Acquisition Regulation. If the government contemplates the award of a cost type contract, the offeror must demonstrate prior to award that its accounting system is adequate for administering a cost-reimbursement contract. The Government may also elect to make Other Transactions (OT) agreements.

References

1. Kuiken, T et al., Curr. Opinion Virol. 2012, 2:276-286. DOI:10.1016/j.coviro.2012.02.013.
2. D'Elia, RV et al., Clin. Vaccine Immunol. 2013, 20(3):319. DOI:10.1128/CVI.00636-12.