

## ATTACHMENT 1

### STATEMENT OF WORK (SOW)

#### Introduction/Background

The Department of Health and Human Services (HHS), Biomedical Advanced Research and Development Authority (BARDA) and the Office of Acquisitions Management, Contracts & Grants (AMCG) seeks to establish a program for the advanced development of broad-spectrum influenza monoclonal antibodies that will reduce the morbidity and mortality associated with influenza infection in severely ill hospitalized patients. 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 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 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 support approval pathways for new classes of antiviral drugs and therapies that will be less susceptible to viral resistance.

#### Reports/Policy Documents

- The National Strategy for Pandemic Influenza (November 2005)
- Pandemic All-Hazard Preparedness Act of 2006 (PL 109-417)
- Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PL 113-5)
- Implementation Plan for the National Strategy for Pandemic Influenza (May 2006)
- Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Implementation Plan (December 2012)

#### Scope and Requirements

Independently and not as an agent of the government, the Contractor shall furnish all the necessary services, qualified personnel, materials, equipment, and facilities not otherwise provided by the government as needed to perform the work necessary to develop and file for license a broad-spectrum influenza monoclonal antibody candidate that meets the Key Attributes listed below:

- An indication for the treatment of seriously ill, hospitalized patients 6 months and older who are infected with influenza.
- Broad-spectrum neutralizing activity across multiple subtypes of influenza A viruses including but not limited to contemporary strains of H1N1, H3N2, H5N1 and H7N9.

- Single dose treatment regimen consisting of a formulation that contains no more than three monoclonal antibodies.
- Effective when treatment is initiated within 48-96 hours of influenza symptom onset (72-96 hours preferred).
- Suitable for use in combination with other approved influenza antivirals.

The contractor shall provide details of the activities necessary to fully develop their proposed broad-spectrum influenza monoclonal antibody candidate. The work plan outlined by the contractor for the project should not exceed five years while achieving the following objectives.

**Objective 1:** Advanced development of a broad-spectrum influenza monoclonal antibody candidate for U.S. licensure to treat influenza infections. Necessary activities should be proposed by the contractor, but may include the following:

1. Clinical trials
  - a. A phase 2 clinical study to evaluate safety and select an appropriate dose for pivotal studies.
  - b. Phase 3 pivotal studies for the treatment of influenza infection in patients at high risk of progressing to severe disease and/or severely ill, hospitalized patients.
  - c. Clinical studies for expanding the indication to the elderly and pediatric populations.
  - d. Additional Phase 1 studies necessary for product licensure.
2. Manufacturing
  - a. Process optimization and validation
  - b. Process scale up
  - c. Manufacturing of clinical and registration lots
3. Additional pre-clinical studies
  - a. Additional animal efficacy studies
  - b. Long-term toxicology studies
4. Regulatory activities
  - a. Regulatory filings and meetings with the FDA
  - b. BLA preparation

**Objective 2:** Development of comprehensive milestone-driven Product Development Plans for a broad-spectrum influenza monoclonal antibody candidate. The Plans must be inclusive of activities performed and completed prior to contract award and those pre-clinical, clinical, manufacturing and regulatory activities to be performed post-contract award.

**Objective 3:** Development of an Earned Value management System (EVMS) to integrate EVMS consistent with ANSI/EIA standard-748 into the monthly progress reports.

## **Milestones**

Milestone 1: Within three (3) months of contract award, the Contractor shall provide to HHS for review and acceptance a comprehensive milestone-driven Product Development Plan for a broad-spectrum influenza monoclonal antibody candidate. The Plan must be inclusive of pre-clinical and clinical activities performed and completed prior to contract award and those pre-clinical, clinical, manufacturing and regulatory activities to be performed post-contract awarding. The Plan shall be a high-level overview and include the following:

- A. A Gantt chart timeline or equivalent.
- B. A description of the process development and scale-up of monoclonal antibody manufacturing.
- C. A description of non-clinical toxicology studies.
- D. A description of clinical and consistency lot manufacturing for FDA product approval.
- E. A description of the general clinical development plan including development and validation of clinical sample assays.
- F. A description of product lot release assay development including lot release product assay specifications and validation.
- G. A complete regulatory master plan that details the pathway to product licensure.

Milestone 2: Within six (6) months of contract award, the Contractor shall submit to HHS for review and acceptance, a comprehensive, integrated Clinical Development and Regulatory Plan. The following issues shall be addressed in the Plan:

- A. A summary of all communication with Center for Drug Evaluation and Research (CDER) at FDA should be incorporated as an appendix to the milestone report.
- B. A detailed description of clinical evaluation shall be integrated with the manufacturing plans using the most current and available information including consultation with CDER. Clinical trials performed as a result of this solicitation shall include any clinical trials necessary to achieve U.S. regulatory approval. Clinical trials should be designed to support licensure for severely ill hospitalized patients 6 months and older who are infected with influenza. Given the duration, cost, and importance of clinical trials, the plan for each clinical trial must clearly indicate key outcomes, populations, study sites and collaborators, analytic strategy, sample size, timelines, and other key components. Studies shall be included demonstrating that the proposed candidate meets all of the Key Attributes. A detailed description of clinical lot manufacturing results, provisional lot release specifications, completed Phase 1 trials and any additional stages of product development that have been completed should be incorporated as an appendix to the milestone report.
- C. A detailed description of regulatory activities shall be integrated with all products, clinical testing and manufacturing activities using the most current and available information, including consultation with CDER. A risk assessment and mitigation plan addressing manufacturing, clinical and regulatory obstacles that may prevent or delay licensure must be included. Issues suitable for risk assessment include expression systems and cell lines, assay development, process yields and facility management. Mitigation plans should include decision trees where applicable.

Milestone 3: Within twelve (12) months of contract award, the Contractor shall provide HHS for review and acceptance a Feasibility Plan to manufacture, test, and release product containing the monoclonal antibody candidate. The Plan should include the following elements:

- A. A process description, including a summary of process data that describes the yield of active product ingredient (API) and final product, addition of any excipients and purification efficiencies of key process steps.
- B. A comparison of process data that describes the significance of process scale-up and yield/purity comparisons after scale-up.
- C. Proposed production schedules including detailed timelines for each development step, conception of a manufacturing scheme, manufacture of proposed clinical lots, description of scale-up plans and manufacturing plant needs, receipt timelines for any virus strains that need importation clearance, QA/QC guidance and timelines, FDA inspection and clearance of manufacturing facilities and building or retrofitting schedules for manufacturing facility(s).
- D. A bulk and fill-finish manufacturing capacity analysis.
- E. A description of process optimization activities.
- F. Dose calculations and contingency plans to address the need for higher dosages of the API.

Milestone 4: Contractor Defined Milestones. The Contractor shall provide a work breakdown structure including comprehensive and integrated timelines (Gantt chart) and major milestones to complete the remaining scope of work as relevant given the stage of drug development and evaluation toward product licensure. The Contractor shall propose milestones, at which time data will be presented, summarizing results of prior activities and new plans and protocols that will be submitted for review and approval in order to guide all subsequent activities. Potential milestones may include manufacturing of an investigational lot of drug, validation of facilities, systems and equipment, validation of Quality Control product lot release methods, validation of manufacturing processes, stability study programs, consistency lot manufacturing, completion of a clinical trial and progress to a new phase of drug evaluation, submission of a license application, etc.

Milestone 5: Earned Value Management. An Earned Value Management System (EVMS) will be required of the Contractor. The Contractor will include a plan in the proposal to integrate EVMS consistent with ANSI/EIA standard-748 into its monthly progress reports (FAR 52-234-4). Both parties will take the needed measures to ensure the EVMS employed is understood by the Contractor and that personnel are assigned for its goals, function and maintenance. To accomplish this, an initial IBR will be conducted and annual validation and surveillance reviews may be utilized throughout the life of the contract.