Broad Agency Announcement (BAA) for the Advanced Research and Chemical, Biological, Radiological, and Nuclear (CBRN) Medical Countermeasures for BARDA

BAA-16-100-SOL-00001

Biomedical Advanced Research and Development Authority

(BARDA)

330 Independence Avenue, SW, Room G644

Washington, DC 20201

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INTRODUCTION

This Broad Agency Announcement (BAA), which sets forth research areas of interest for the Biomedical Advanced Research and Development Authority (BARDA), is issued under paragraph 6.102(d)(2)(i) of the Federal Acquisition Regulation (FAR). Proposals selected for award are considered to be the result of full and open competition and in full compliance with "The Competition in Contracting Act of 1984" 41 U.S.C. § 251 et seq. A formal Request for Proposal and/or additional information regarding this announcement will not be issued. Paper copies of this announcement will not be issued. The Government reserves the right to select for award and fund all, some or none of the proposals in response to this announcement. All proposals will be treated as sensitive competitive information and the contents only disclosed for the purpose of evaluation.

Offerors that are not responsive to BARDA requests for information in a timely manner, defined as meeting government deadlines established and communicated with the request, may be removed from award consideration.

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.

OVERVIEW INFORMATION

Agency Name:

Department of Health and Human Services, Office of the Secretary, Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority 330 Independence Avenue, SW, RM G644, Washington, DC, 20201

Issuing Office:

Department of Health and Human Services, Office of the Secretary, Assistant Secretary for Preparedness and Response, Acquisition Management, Contracts & Grants (AMCG), 330 Independence Avenue, SW, RM G644, Washington, DC, 20201

Research Opportunity Title:

BARDA Broad Agency Announcement for the Advanced Research and Chemical, Biological, Radiological, and Nuclear (CBRN)

Announcement Type and Date:

Broad Agency Announcement renewal announcement, October 1, 2015 as: BAA-16-100-SOL-00001

Note: This Broad Agency Announcement is a re-issuance of the following versions which have been re-issued annually:

Initial Announcement as BARDA CBRN BAA-09-34, issued March 4, 2009 Renewed March 4, 2010 as BARDA CBRN BAA-10-100-SOL-00012 Renewed March 4, 2011 as BARDA CBRN BAA-11-100-SOL-00009 Renewed June 8, 2012 as BARDA CBRN BAA-

12-100-SOL-00011. Renewed July 31, 2013 as BARDA CBRN BAA-13-100-SOL-00013.

This BAA is available on the following websites:

- Federal Business Opportunities - FBO.gov[1]
- MedicalCountermeasures.gov[2]
- Public Health Emergency - PHE.gov[3]
- Grants.gov[4]

Amendments to this BAA will be posted to the websites listed above when they occur. Interested parties are encouraged to periodically check these websites for updates and amendments.

Eligible Offerors:

This BAA is open to **ALL** responsible sources. Offerors may include single entities or teams from private sector organizations, Government laboratories, and academic institutions.

To be eligible for award, a prospective recipient must meet certain minimum standards pertaining to financial resources, ability to comply with the performance schedule, prior record of performance, integrity, organization, experience, operational controls, technical controls, technical skills, facilities, and equipment.

Federally Funded Research and Development Centers (FFRDCs) and Government entities (Government/National laboratories, military educational institutions, etc.) are subject to applicable direct competition limitations and cannot propose to this BAA in any capacity unless they address the following conditions. FFRDCs must clearly demonstrate that the proposed work is not otherwise available from the private sector AND must also provide a letter on letterhead from their sponsoring organization citing the specific authority establishing their eligibility to propose to government solicitations and compete with industry, and compliance with the associated FFRDC sponsor agreement and terms and conditions. This information is required for FFRDCs proposing to be prime or subcontractors. Government entities must clearly demonstrate that the work is not otherwise available from the private sector and provide written documentation citing the specific statutory authority (as well as, where relevant, contractual authority) establishing their ability to propose to Government solicitations. Specific supporting regulatory guidance, together with evidence of agency approval will be required to fully establish eligibility. BARDA will consider eligibility submissions on a case-by-case basis; however, the burden to prove eligibility for all team members rests solely with the Proposer.

Historically Black Colleges and Universities (HBCU), Minority Institutions (MI), Small Business concerns, Small Disadvantaged Business concerns, Women-Owned Small

[1] https://www.fbo.gov/
[2] https://www.medicalcountermeasures.gov/
[3] http://www.phe.gov/
[4] http://www.grants.gov/

Business concerns, Veteran-Owned Small Business concerns, Service-Disabled Veteran-Owned Small Business concerns, and HUB Zone Small Business concerns are encouraged to submit proposals and to join other entities as team members in submitting proposals.

In accordance with federal statutes, regulations, and HHS policies, no person on grounds of race, color, age, sex, national origin, or disability shall be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving financial assistance from the HHS.

Research Opportunity Description:

The Biomedical Advanced Research and Development Authority solicits the advanced research and development of medical countermeasures for chemical, biological, radiological, and nuclear agents that threaten the U.S. civilian population. BARDA anticipates that research and development activities awarded under this BAA will serve to advance candidate medical countermeasures towards FDA licensure/approval and consideration for acquisition.

The purpose of this BAA is to solicit proposals that focus on one or more of the following solicited areas of interest as listed here and further described in Part I of this announcement.

Research Areas of Interest:

1. Vaccines
2. Antitoxins and Therapeutics Proteins
3. Antimicrobial Therapeutics
4. Radiological / Nuclear Threat Medical Countermeasures
5. Chemical Threat Medical Countermeasures
6. Clinical Diagnostics

Research and technical objectives are described in Part II and efforts proposed by Offerors may include activities in Non-Clinical Research and Development, Process Development, Formulation, and Manufacturing Development, and Clinical Evaluation.

Technological Maturity:

Offerors must identify in their Quad Chart and White Paper the current Technology Readiness Level (TRL) of their product, and the TRL level identified should meet or exceed the requirements of the given Research Area of Interest. Each White Paper should also contain sufficient supporting information to justify the TRL rating. Criteria for determining the appropriate TRL level for a product can be found in Attachment 1. Note that all activities within a TRL level (or sublevel) must be completed to have achieved that TRL status. One TRL criteria document is provided for use with diagnostics and medical devices (Attachment 1A) and one TRL criteria document is provided for use with drugs and biologics (Attachment 1B).

Number of Awards:

Multiple awards of various values are anticipated and are dependent upon the program

priorities, proposals' scientific/technical merits, how well the proposals fit BARDA's areas of interest, and available funding. Anticipated funding for the program (not per contract or award) may range from $2M to $415M dollars subject to congressional appropriations. This funding profile is an estimate only and will not be a contractual obligation for funding. All funding is subject to change due to government discretion and funding availability.

Type of Award:

A contract awarded under this BAA may utilize: Cost-Reimbursement, Cost-plus-fixed-fee (CPFF), Cost-plus-incentive-fee (CPIF), Firm fixed price (FFP), a cost sharing structure. Although cost sharing is not required under this BAA; however, formal or informal cost sharing is encouraged where there is a reasonable probability of a potential commercial application related to the proposed research and development effort.

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. Offerors should propose the type of arrangement they believe best satisfies the requirement.

BARDA may also elect to make awards in the form of grants and cooperative agreements, and Other Transactions (OT) agreements, as authorized for BARDA under the Pandemic and All Hazards Preparedness Reauthorization Act (2013).

The costs of preparing responses to this BAA are not considered an allowable direct charge on any resultant award.

Application Process:

Stage 1: Prepare a cover sheet, Quad Chart, and White Paper in accordance with the preparation guidance. The Quad Chart and White Paper should describe the effort in sufficient detail to allow evaluation of the concept's technical merit and its potential contribution to the BARDA mission. BARDA will evaluate White Papers based on the criteria provided in Part VII.

Offerors whose Quad Chart and White Paper receive a favorable evaluation will be invited by e-mail to submit a Full Proposal. Offerors whose Quad Chart and White Paper did not receive a favorable evaluation will be notified by e-mail, and will be provided with information on technical issues and concerns that BARDA has regarding the proposed product. This written feedback is the only response that will be provided to unsuccessful Stage 1 Offerors.

Stage 2: Offerors must submit their Full Proposals in accordance with the instructions provided Part VI. Full Proposals will be evaluated against criteria as described in Part VII. Proposals that do not conform to the requirements outlined in the BAA or to the instructions provided in the invitation letter will not be considered for further action.

Submission Deadlines and Government Response Time(s):

Table 1: Submission Deadlines and Government Response Time

Proposal Stage	Deadline for Submission*	USG Response
Stage 1: Quad Chart and White Paper	Areas 1, 2,3, 6: 30-Jan-2016 30-Apr-2016 30-Jul-2016 30-Oct-2016 30-Jan-2017 30-Apr-2017 30-Jul-2017 30-Oct-2017 Areas 4,5: Open for continuous submission, subject to the BAA expiration date. The final White Paper deadline is October 30, 2017.	Areas 1, 2, 3, 6: Invitation letters sent 90 days from submission of the next interim or final deadline following White Paper submission Areas 4, 5: Invitation letters sent 90 days from submission.
Stage 2: Full Proposal	As specified in the invitation Letter	As specified in the invitation letter
Source Selection Notification (pending availability of funds)		Decision within 180 calendar days of receipt of Full Proposal or final revised proposal.

*Submissions are due each date at 4:30PM EST. Receipts for all White Papers submitted will be sent electronically within one (1) week of submission.

Contact/Submission Information:

All submissions and administrative inquiries regarding this BAA shall be addressed to CBRN-BAA@hhs.gov.

Technical questions should be directed to the Technical Point of Contacts (POCs) shown following each research areas of interest. These POC's are located, in "Part I: Research Areas of Interest." When an inquiry is made, please include all pertinent contact information.

Be advised that after a white paper (or full proposal) has been submitted, all communications related to that submission must be through the BARDA

Contracting Office AMCG.

As a white paper is not considered a "proposal," no debriefing will be provided defined by FAR Subpart 15.5.

Quad Chart and White Papers WILL NOT BE ACCEPTED after 4:30 PM (Eastern Standard Time) on 30 September 2017. The submission deadlines are listed below.

Preliminary Inquiries:

BARDA realizes that the preparation of a development proposal often represents a substantial investment of time and effort by the Offeror. In an attempt to minimize this burden, BARDA encourages organizations and individuals interested in submitting development proposals to make preliminary inquiries as to the general need for the type of development effort contemplated before expending extensive effort in preparing a detailed development proposal or submitting proprietary information.

Offerors contemplating submitting Quad Charts, White Papers, and Full Proposals are strongly encouraged to contact the appropriate technical Point of Contact (POC) at BARDA (see names and e-mail addresses listed immediately after each research area of interest). Offerors are advised that only a Contracting Officer may obligate the Government to any agreement involving expenditure of Government funds.

TechWatch Program:

Offerors under this BAA are invited to arrange a meeting at BARDA headquarters through the TechWatch program. Participation in the TechWatch program affords offerors an opportunity to present their capabilities to BARDA scientific subject matter experts and program managers, as well as AMCG contract professionals. These personnel can evaluate products/technologies, suggest techniques and strategies for meeting technical and regulatory challenges, provide insight on how a product or technology may address BARDA's objectives, and provide general information about BARDA's mission and programs. To arrange a TechWatch meeting and for more information about the TechWatch program, offerors should visit the TechWatch website[5]. Please allow sufficient time for BARDA to schedule a meeting with your organization. Entities with a white paper or proposal currently under review under any ASPR solicitation are not eligible to schedule a TechWatch meeting related to that submission.

Special Instructions:

Special instructions will be advertised via the BAA as they become apparent. These additional instructions are tailored to a specific area of interest and may have a unique submittal date. The information requested in these instructions should be used along with Part VI of the BAA to format and prepare the Technical and Cost Proposals. Offerors should follow the instructions in Part VI of the BAA, and include the information requested therein.

Proposal Handling and Submission Information:

[5] https://www.medicalcountermeasures.gov/barda/advancing-innovation/techwatch.aspx

Treatment of Submission Documents: All proposals are treated as offeror's proprietary information prior to award and the contents are disclosed only for the purpose of evaluation. The Offeror must indicate any limitation to be placed on disclosure of information contained in the proposal in accordance with the instructions as set forth by FAR 52.215- 1(e) "*Restrictions on disclosure and use of data," and outlined in the Attachments to this BAA.*

CLASSIFIED SUBMISSIONS: Classified proposals will not be accepted. All submissions must be Unclassified.

Use of Color Proposals: All proposals received shall be stored as electronic images. Electronic color images require a significantly larger amount of storage space than black-and- white images. As a result, Offerors' use of color in proposals should be minimal and used only when absolutely necessary for details. Do not use color unless necessary.

Post Employment Conflict of Interest: There are certain post employment restrictions on former federal officers and employees, including special government employees (Section 207 of Title 18, U.S.C.). If a prospective Offeror believes a conflict of interest may exist, the situation should be emailed to the appropriate Contracting Officer, prior to expending time and effort in preparing a proposal. The appropriate HHS personnel will discuss any conflict of interest with prospective Offeror.

Unsuccessful Proposal Disposition: Proposals will not be returned. The original of each proposal received will be retained by ASPR pursuant to FAR 4.805 and all other non-required copies destroyed.

Government Notice for Handling and Submitting Proposals: Refer to Attachment 6 for inclusion requirement of the government notice.

BACKGROUND

BARDA, the lead federal agency for supporting advanced development of medical countermeasures (MCM) to address CBRN threats for the civilian population, is located within the Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS). BARDA is soliciting proposals for the advanced research and development of MCM for chemical, biological, radiological, and nuclear (CBRN) agents that threaten the U.S. civilian population. The continuing threat of terrorism underscores the compelling need to develop new and improved MCM for protecting all segments of the civilian population. This BAA will support the development of candidate products and diagnostic tools to meet the challenging requirements of CBRN MCM (e.g. post- exposure efficacy, extended shelf life, storage, distribution, and dispensing). Contracts resulting from this BAA may also benefit from multiple core services that BARDA provides already, and will provide, in the future. These core services include an animal study network, flexible manufacturing facilities, and technical expertise in development, manufacturing, regulatory affairs, quality systems, and clinical studies.

BARDA's priorities are aligned with the preparedness mission of the HHS Public Health

Emergency Medical Countermeasures Enterprise (PHEMCE), as articulated in the 2012 PHEMCE Strategy and Implementation Plan[6]. Specifically, HHS has generally adopted a strategy of developing and acquiring medical countermeasures for post-event response to CBRN threats. Preventive measures are appropriate only for threats of such potential catastrophic consequence that a pre-event strategy will be examined in order to reduce vulnerability and mitigate post-event consequences. Currently, no pre-event MCM strategies are deemed necessary and feasible at this time for the U.S. civilian population. Therapeutics and diagnostics or the use of post-event prophylaxis will be the preferred strategy for all other threats. Priority will be placed on medical countermeasures that focus on post-event prophylaxis or post-exposure treatment. Some CBRN programs are reaching maturity and their intended goal, and receive less emphasis in this process. More emphasis will be placed upon product candidates that have multi-purpose indications (i.e. CBRN usage and commercial indication for public health needs). Additional focus will be placed on supporting the development of medical countermeasures suitable for use in special populations such as children, pregnant women, the elderly, and persons with compromised immune systems, prioritizing and supporting projects that provide benefits to all populations where possible and exploring focused development projects or studies where necessary. To that end, BARDA supports the advanced research/development and acquisition of MCM such as vaccines, therapeutics, and diagnostics.

BARDA strives to drive innovation in support of the underlying capabilities necessary to develop and manufacture medical countermeasures that align with the BARDA mission and PHEMCE goals. As such, BARDA is interested in the implementation of Continuous Manufacturing (CM) processes for advanced development of therapeutics. CM is the integration of multiple unit operations into a single end-to-end system based on model control that allows for constant reagent influx and respective outflow of product. Although CM is not required for successful proposal submission, BARDA is particularly interested in CM development and use for existing BARDA funded products and new potential product candidates where there can be a measurable impact on efficiencies compared to traditional batch manufacturing. This may include, but are not limited to, improvements in rate and yield of production, reagent usage, process steps, facility footprint and economic return. Potential offerors are encouraged to consider incorporating aspects of CM into their product development plan. Proposals may include CM technology development or improvements as well as preliminary steps to evaluate the feasibility of CM as compared to traditional batch processes.

For additional requirements information:

- The Pandemic and All Hazard Preparedness Act[7] Pub. L. No. 109-417, 42 U.S.C. § 241 et seq. (PAHPA) and

- The Pandemic and All Hazard Preparedness Reauthorization Act Pub. L. No. 113-5[8], (PAHPRA) authorizes BARDA to (i) conduct ongoing searches for, and support calls for, potential qualified countermeasures and qualified pandemic or epidemic products; (ii) direct and coordinate the countermeasure and product advanced research and development activities of the Department of Health and

[6] https://www.medicalcountermeasures.gov/media/13962/2012-phemce-implementation-plan.pdf
[7] http://www.gpo.gov/fdsys/pkg/PLAW-109publ417/pdf/PLAW-109publ417.pdf
[8] http://www.gpo.gov/fdsys/pkg/PLAW-113publ5/pdf/PLAW-113publ5.pdf

Human Services; (iii) establish strategic initiatives to accelerate countermeasure and product advanced research and development (which may include advanced research and development for purposes of fulfilling requirements under the Federal Food, Drug, and Cosmetic Act or section 351 of this Act) and innovation in such areas as the Secretary may identify as priority unmet need areas; and (iv) award contracts, grants, cooperative agreements, and enter into other transactions, for countermeasure and product advanced research and development.

Learn more about legal authorities, policies, and committees[9] and strategies and reports[10] for Chemical, Biological, Radiological, and Nuclear Medical Countermeasures.

[9] http://www.phe.gov/preparedness/legal/Pages/default.aspx
[10] https://www.medicalcountermeasures.gov/federal-initiatives/strategies-and-reports.aspx

Part I: Research Areas of Interest

This section presents an overview of the CBRN-related research and development projects that BARDA seeks to support through this BAA. Each Offeror should also review Part II: Technical Objectives.

Offerors contemplating submitting quad charts and white papers are strongly encouraged to contact BARDA technical point of contact for the respective area of interest. Be advised that after a white paper (or full proposal) has been submitted, all communications related to that submission must be through the ASPR's Office of Acquisitions Management, Contracts, and Grants (AMCG).

Area of Interest #1: Vaccines

1.1 **Advanced development projects for next generation anthrax vaccines** that provide significant advantages over the currently licensed Anthrax Vaccine Absorbed (AVA), including one or more of the following:

- Fewer doses to protection
- Faster protective immune response
- Improved storage conditions (e.g. no cold chain)

The proposed vaccine candidate (final formulation) must have 12 months of stability data as measured by acceptable stability indication assay. Preference will be given to candidate products where the final vaccine formulation has demonstrated comparability, non-inferiority preferred, to the current licensed anthrax vaccine in a non-clinical, lethal challenge study as measured by survival and immunological response by toxin Neutralization Assay (TNA). The study to show comparability or non-inferiority will be in a single, well designed study. Preference also will be given to vaccine candidate (final formulation) with an active IND and human safety data at time of submission.

1.2 **Advanced development projects for vaccines against Ebola and Marburg viral hemorrhagic fevers**. The proposed vaccine candidate must have demonstrated protection from lethal challenge in non-clinical animal studies, with preference given to candidate products with data from non-human primate studies. Preference will also be given to candidate products with one or more of the following:

- multivalent vaccine
- safety toxicity data
- preliminary formulation
- stability indicating assay
- demonstrated small scale manufacturing process

The objective of this program is to advance projects through the end of Phase 2 clinical development. Offerors are encouraged to meet with BARDA through the TechWatch

mechanism prior to submitting a white paper. Learn more about requesting a TechWatch meeting[11].

1.3 **Programs to expand availability of licensed anthrax and smallpox vaccines for at risk populations**, e.g. pediatric populations. Interested parties should refer to the Presidential Commission for the Study of Bioethical Issues report on Safeguarding Children: Pediatric Medical Countermeasures Research[12] report.

1.4 Submissions for smallpox vaccines will not be considered during the open period of this BAA, unless specifically announced through special instructions.

Technical Point of Contact: Dr. Eric Espeland; eric.espeland@hhs.gov

Area of Interest #2: Antitoxins and Therapeutic Proteins

2.1 **Development of peptide or small molecule antitoxins, and other novel compounds, with innovative formulations offering enhanced long-term stability.** The candidate must be at TRL-6 (active IND and human safety data).

2.2 **Development of antibody treatments and other therapeutic agents for viral hemorrhagic fevers viruses**. Programs must be at TRL-5 with a lead candidate identified.

Technical Point of Contact: Dr. Chia-Wei Tsai chia-wei.tsai@hhs.gov

Area of Interest #3: Antimicrobial Therapeutics

In accordance with the Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006 reauthorized in 2013 (PAHPRA), BARDA has the responsibility to ensure that the United States has a sufficient supply of vaccines and drugs to respond to public health emergencies caused by pandemic influenza, emerging infectious diseases, and chemical, biological, and radiological and nuclear threats. BARDA recognizes the dual utility of antimicrobials for the treatment and prevention of diseases caused by bacterial and viral threat agents, and clinically relevant emerging and drug resistant pathogens. Moreover, in accordance with the National Strategy for Combating Antibiotic-Resistant Bacteria and the Executive Order on Combating Antibiotic Resistant Bacteria, BARDA aims to form public-private partnerships to accelerate research and development of new antimicrobial therapeutics for the treatment or prevention of infections. Of particular interest to the Government are proposals which aim to:

3.1 Develop and test antibacterial products that are in advanced development for post-exposure prophylaxis (PEP) and treatment efficacy against one or more biodefense threat agents (Bacillus anthracis, Yersinia pestis, Francisella tularensis, Burkholderia mallei, and Burkholderia pseudomallei). Minimum inhibitory concentration (MIC) data for multiple strains of each threat agent bacterial species under consideration is required; larger data sets (e.g. MIC90 calculations) will strengthen the proposal.

3.2 Develop new small molecule drugs that treat or prevent resistant microbial infections either alone or in combination with another therapeutic;

[11] https://www.medicalcountermeasures.gov/Request-Meeting.aspx
[12] http://bioethics.gov/sites/default/files/PCSBI_Pediatric-MCM508.pdf

3.3 Develop non-traditional antibacterial therapeutics that treat or prevent resistant infections either alone or in combination with another therapeutic. Examples include, but may not be limited to, antibody-based approaches, host-directed therapies including immunomodulators, antimicrobial peptides, phage, microbiome approaches; and approaches to inhibit quorum sensing and expression of bacterial virulence factors.

Products should possess activity against one or more of the pathogens categorized as serious, urgent, or concerning threats in the September 2013 CDC Report titled Antibiotic Resistance Threats in the United States, 2013. Competitiveness will be enhanced if the proposed product(s) possess activity against Gram negative pathogens. Products may also be assessed for the treatment or prevention of biothreat agent infection.

Under this area of interest, most aspects of drug development are considered permissible including clinical studies, nonclinical studies, safety, toxicology, PK/PD and microbiological studies, manufacturing, analytical assay development and validation, regulatory submission preparation, and the use of diagnostics to enhance clinical trial enrollment.

Qualities that strengthen the competitiveness of a proposal include:

- Substantial improvements over existing antimicrobial products, novel first in class compounds with unprecedented robust mechanisms of action are urgently needed. If a compound belonging to an existing class (same/similar chemistry and pathogen target) of antimicrobial products is proposed, there must be significant advantages such as overcoming existing resistance mechanisms and/or greatly improved therapeutic properties.

- Greater technological advancement of the lead compound: Successive progression through TRL levels and corresponding completion of commercial drug development activities will increase the attractiveness of proposals - Data from IND enabling toxicology studies is a requirement improved upon by having filed an IND, and further made attractive with progression into and completion of Phase 1, 2, and 3 clinical studies.

- Regulatory feasibility: Evidence of supportive responses from the FDA concerning the development plan of the drug will reduce risk to a potential investment by BARDA.

- Special populations: Antimicrobials that offer therapeutic benefit to special populations, particularly pediatric subjects, are an important and underserved area. Proposals that have specific plans, likely utility, and proposed activities to advance a product for approved use in special populations will be viewed more favorably.

- Cost sharing: Proposals that demonstrate a commitment of resources from the Offeror in the form of sharing the cost of the proposed development plan are most advantageous.

Learn more about Broad Spectrum Antimicrobial[13].

Technical Point of Contact: Dr. Melissa Stundick; melissa.stundick@hhs.gov

Area of Interest #4: Radiological/Nuclear Threat Medical Countermeasures

Concept of Operations (CONOPs) for Radiological and Nuclear Incidents

The current thinking for an emergency response to a radiological/nuclear event suggests two general phases of treatment:

a. **Field Care**: This treatment phase is generally defined as the first 72 hours of the emergency response. The primary goal is to provide life-saving interventions and immediate care where necessary. Treatment will likely be administered at or near the incident site or at peripheral assembly sites for evacuation. Resources and trained personnel are expected to be exceedingly scarce. MCMs should be compatible with the published RTR medical response system (*Prehosp Disaster Med*. 2009 May-Jun; 24(3):167-78).

   - Emphasis is placed on the following MCM qualities:
     - o Ease of administration
     - o High therapeutic index
     - o Robust storage, ease of deployment
   - The current area of interest scope does not currently include the development of field use anti-neutropenics.

b. **Definitive Care**: This treatment phase extends beyond the initial 72 hours of the emergency response. The primary goal is to fully manage a patient's condition. This includes the full range of preventive, curative, acute, convalescent, restorative, rehabilitative and palliative medical care. Treatment will primarily be administered at medical centers and hospitals operating at surge capacity. Though resources and trained personnel are expected to be strained, their scarcity will not be as severe as that of the Field Care phase.

BARDA's interest is in the development of specific medical countermeasures to mitigate or treat sub-syndromes of Acute Radiation Syndrome (ARS) and the Delayed Effects of Acute Radiation Exposure (DEARE), blood products, and treatments for severe thermal burns. The list does NOT reflect prioritization.

Radiological and Nuclear Programmatic Priorities

Based on the near-, mid-, and long-term objectives for radiological and nuclear threats prescribed by the 2014 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan[14] (p. 80-81), BARDA is interested in the following programmatic areas for Area of Interest #4:

[13] https://www.medicalcountermeasures.gov/barda/cbrn/broad-spectrum-antimicrobials.aspx
[14] http://www.phe.gov/Preparedness/mcm/phemce/Documents/2014-phemce-sip.pdf

4.0 Acute Radiation Syndrome (ARS) and the Delayed Effects of Acute Radiation Exposure (DEARE): “BARDA will support evaluation of a number of commercial drugs for repurposing to enable use in the treatment of exposure to radiological and nuclear agents, ensuring that at-risk population needs are considered.

BARDA will also support the advanced research and development of novel compounds for PEP (post-exposure prophylaxis) and treatment of exposure to radiological and nuclear threats.

4.1 Development of mitigators or treatments for subsyndromes associated with Acute Radiation Syndrome (ARS) and the Delayed Effects of Acute Radiation Exposure (DEARE), arising from exposure to ionizing radiation. The subsyndromes of current interest to BARDA are the thrombocytopenia component of the hematopoietic subsyndrome and the gastrointestinal subsyndrome. Proposals that address these areas will be given higher priority over proposals addressing other subsyndromes. Additionally, proposed MCMs that target underlying pathophysiological endpoints with a clear etiology to the prioritized subsyndromes are also of interest. The technical readiness level for candidates should be at TRL 5 or higher for an ARS or DEARE indication (i.e., completed all activities described for TRL 5); Offerors should have held a pre-IND meeting with FDA to discuss licensure as an MCM prior to the submission of a white paper to the BARDA BAA and should be prepared to provide the minutes from the meeting, if requested. Treatments that have efficacy when administered 24 hours or more post irradiation are of particular interest. For clarity, ALL of the following activities should be completed prior to submission: Assays: Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate; Manufacturing: Initiate process development for small-scale manufacturing amenable to GMP; Target Product Profile: Draft preliminary Target Product Profile. Shelf life, storage conditions, and packaging should be considered to ensure that anticipated use of the product is consistent with the intended use for which approval will be sought from FDA; TRL 5A: Demonstrate acceptable Absorption, Distribution, Metabolism and Elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing; TRL5B: Continue establishing correlates of protection, endpoints, and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose once clinical data are obtained. Submissions not meeting the TRL 5 maturity requirement will not be reviewed.

In addition, development of mitigators and treatments of other radiological/nuclear incident related medical treatment gaps (e.g., blood products) are also covered under this area of interest.

The current area of interest scope does not currently include the development of field use anti-neutropenics.

Decorporation Agents

BARDA will continue to fund projects to support advanced research and development of Prussian blue formulations appropriate for children under the age of two years.

4.2 Development of decorporation agents which are either passive (limited generally to the blood pool) or active chelators (preferred; seeks intracellular or distributed depots)

for these isotopes of interest: Co-60, Sr-90, Cs-137, Ir-192, U-235/238, Pu-238/239, and Am-241, other transuranics are of interest but not a priority and are negotiable as secondary efficacy).

Technical Point of Contact: Dr. Mary J. Homer; mary.homer@hhs.gov

Thermal Burn MCM

4.3 Development of mitigators or treatments for thermal burn injuries, arising from exposure to the detonation effects of improvised nuclear devices or (INDs) along with ionizing radiation. The technical readiness level for candidates should be at TRL 5 or higher (i.e. completed all activities described for TRL 5); Offerors should have held a pre-IND or pre-IDE or pre-submission meeting with FDA to discuss licensure/clearance/approval as an MCM prior to the submission of a white paper to the BARDA BAA. BARDA may request documentation to support proof of a pre-IND meeting being held and resulting minutes from the agency. Treatments that have efficacy when administered during Definitive Care (as defined above 72 hours post-exposure) are of particular interest.

Thermal burn product categories include Autologous-based, Natural or Manufactured Biologicals, and Ancillary products which enable or enhance the efficacy of treatment. Ideal products would have market sustainability via clinical indications in conventional care and also address one or more treatment goals in Definitive Care for thermal burns as listed below:

Temporize burn injuries and/or limit burn wound conversion

Aid debridement, excision or visualization of the burn wound depth for quicker and reliable treatment options

Spare autograft; adjunct for autograft to enhance healing, recovery and reduce morbidity

Compatible for use with radiation exposure as demonstrated in a non-clinical model

Technical Point of Contact: Dr. Narayan V. Iyer; narayan.iyer@hhs.gov

Area of Interest #5: Chemical Threat Medical Countermeasures

Area of interest #5 includes medical countermeasures that protect the civilian population from the acute health effects of chemical threats, are easy to administer in a mass-casualty situation, and are rapidly effective as post-exposure therapies. The medical countermeasures (MCMs) should also be safe and effective for the entire population, including infants, children, adolescents, elderly, pregnant women and immunocompromised individuals. The technical readiness level for candidates should be at TRL 4 (i.e. completed all activities described for TRL 4) or higher; in vivo activity and potential for efficacy consistent with the product's intended use (i.e. dose, schedule, duration, route of administration, and route of threat agent challenge) must be demonstrated. Offerors should have submitted a pre-IND package to the FDA for licensure as an MCM prior to the submission of a white paper to the BARDA BAA. Specific areas of interest within Chemical Threat Medical Countermeasures include:

5.1 Nerve Agents:

5.1.1 Development of an antiseizurogenic that can stop seizures at extended times after onset, and/or when the seizures may have become refractory to current drugs.

5.1.2 Development of an improved acetylcholinesterase reactivator to replace pralidoxime chloride (e.g., broad spectrum; centrally acting)

5.1.3 Development of an improved anticholinergic to supplement atropine (longer acting and centrally acting).

5.1.4 Development of new formulations of existing antidotes (more easily administered; faster acting).

5.2 Pulmonary Agents: Development of medical countermeasures, including anti-inflammatory drugs, to prevent and treat lung damage from exposure to agents such as chlorine and phosgene.

5.3 Vesicants: Development of medical countermeasures that limit harmful aspects of exposure to vesicating agents such as sulfur mustard and Lewisite, including topical (skin and eye) and systemic preparations.

5.4 Blood/Metabolic Agents: Development of MCMs to treat acute poisoning from agents such as cyanides and fluoroacetates. Antidotes should be easily administered by first responders and safe in all populations.

5.5 Toxic Industrial Chemicals and Emerging Threats: Development of individual MCMs (therapies) that can be used to treat the effects of multiple chemical threat agents and unconventional threats in response to new population threat assessments.

5.6 Development of easily administered and rapidly effective countermeasures that can be used by first responders dealing with large numbers of exposed individuals. Ease of administration in mass casualty situations should take into account the practical limits of injected medications versus inhaled, intranasal and sublingual administration. These alternative routes may fail if persons have profuse respiratory secretions. Autoinjector intramuscular injection may continue to be a preferred route of administration in many, but not all, circumstances.

5.7 Development of chemical decontamination solutions for use on intact /or injured human skin (improved efficacy compared to soap and water). Proposed solutions must be safe for whole-body use and amenable to use in a mass-casualty situation.

Technical Point of Contact: Dr. Judith Wolfe Laney; judith.laney@hhs.gov

Area of Interest #6: Clinical Diagnostics

Design and production of the system in area of interest #6 must be compliant with U.S. Quality System Regulation (21 CFR Part 820).

Biodosimetry Diagnostics:

6.1 Development of a dosimetry self-assessment tool in order to determine if an individual has been exposed to ionizing radiation at a dose equal to or greater than 2 Gy.

6.2 Biodosimetry Systems: BARDA is interested in advanced development of a rapid point- of-care diagnostic assay for assessing whether an individual's absorbed dose of ionizing radiation was above or below 2 Gy, and/or a centralized high-throughput assay system for determining absorbed doses of ionizing radiation in the range of 0.5 Gy to 10 Gy, that have a robust detection signal from 24 hours post-exposure which persists at least one (1) week. The assay system should provide the assessment of the absorbed dose for biodosimetry applications with high sensitivity and specificity. It is preferred for high throughput assays to be developed/optimized for use with existing diagnostic instrument platforms which have a large number of US Clinical lab placements and for point-of-care platforms to be CLIA- waive-able. Minimum technology readiness: TRL-6. White papers must at a minimum include:

1. Listing of radiation responsive marker(s) and performance data in human and an animal model for each of them.

2. Evidence that a pre-submission meeting has been held with the FDA

3. Instrument and consumable definition and performance data of key components or entire system.

4. Listing of all key team members, identifying who will fill each key skill needed to develop, manufacture, and achieve regulatory approval of the product.

5. Functional prototype instrument and consumables in final form.

6.3. Development of an improvement on the current "gold standard" for assessing absorbed doses of ionizing radiation (the dicentric chromosomal assays (DCA)) in terms of ease of use, time for performance, statistical certainty of dose, improved dose range and biomarker lifespan.

Bio-threat Agent Diagnostics:

6.4 Development of an anthrax diagnostic assay system (may be part of a multi-pathogen panel):

6.4.1 Development, clinical evaluation, and/or FDA clearance/approval of rapid, accurate diagnostic systems for determining a Bacillus anthracis infection (anthrax). These systems should be portable and designed for ease-of-use by non-expert personnel at point-of-care (POC) settings. It is preferred that these POC systems be CLIA-waived/waive-able.

6.4.2 Development, clinical evaluation, and/or FDA clearance of centralized, high-throughput diagnostic assay systems for determining a Bacillus anthracis infection (anthrax). It is preferred for high throughput assays to be developed and optimized for use with existing diagnostic instrument platforms that have a large number of US clinical laboratory placements, for use with at least one FDA-cleared "routine health-care" assay.

Notes:

1) For the above, Offerors should provide adequate feasibility data for both the proposed assays and the platform—demonstrating high analytical sensitivity

(clinically relevant), specificity, reproducibility, linearity and dynamic range in relevant clinical matrices, such as whole blood. Validated-assay packages will receive higher consideration. (Platform performance data may include testing with surrogate agents, e.g. B. cereus, or relevant "routine health-care" assays). BARDA is not interested in white papers or proposals that fail to include convincing feasibility data.

2) Submissions made under the above areas of interest 6.4.1 or 6.4.2 should meet TRL 5 or greater (for a detailed list of TRL definitions for diagnostics development see Appendix 1 of this BAA),

6.5 Development, clinical evaluation, and FDA 510(k) clearance of a lateral flow immunoassay device for the detection of Bacillus anthracis Lethal Factor (LF) in whole blood utilizing USG developed antibodies (LF should be detected as both the protein monomer and as part of the anthrax toxin protein complex (LTx)). Device should be CLIA waived or waivable. The Offeror shall improve the sensitivity of the existing prototype device (currently ~5ng/ml sensitivity for LF) to a >> 2ng/ml sensitivity for LF. The US Government is able to provide small quantities of purified protein and is able to license the hybridomas to the Offeror for the production of antibodies that have been shown to work in a lateral flow device for the detection of LF. Consultation with the USG development team is possible.

6.6 Hardware platform development

6.6.1 In vitro diagnostic (IVD) devices that would provide rapid, accurate point-of-care (POC) / "field-use" testing of the civilian population (including special populations) and results-reporting after a large scale incident resulting in exposure to bio-threat agents of interest. POC platforms should be capable of use at or near the point of need, such as doctors' offices, hospital emergency room labs, or more austere environments such as in a mobile deployable hospital, school gymnasium, or tents near the site of a bio-threat agent incident. Ideally, these devices would be capable of performing bio-threat and routine healthcare-use assays. In addition, these essential elements are sought:

1) Small footprint

2) Ease of use

3) Rapid assay turnaround times, sample to answer results in under 30 minutes (15 minutes preferred)

4) CLIA waived/waive-able

5) Ability to be operated in non-temperature/humidity controlled environments.

6) Low cost

7) FDA clearance

6.6.2 New and innovative sample collection and preparation technologies needed for collecting and processing clinical samples potentially containing biothreat agents of

interest for use at point of care. Samples shall be rendered safe to handle by the device.

Note: Submissions made under the above areas of interest 6.6.1 or 6.6.2 must meet TRL 4 or greater (for a detailed list of TRL definitions for diagnostics development see Appendix 1 of this BAA.

6.7 "Bio-threat Agent of Interest" Knowledge Development:

6.7.1 Characterization of pathogen or disease specific markers and their relationship to the diagnostic window of opportunity and clinical utility in clinical samples. These studies should be designed to show the clinical relevance of the diagnostic assay, including determination of the most appropriate sample type and matrix. If applicable, cite the markers that are intended as starting points for the project, with references.

6.7.2 Assay development of appropriate pathogen or disease specific markers including detection methods to provide greatest diagnostic utility.

6.7.3 Studies to inform the clinical effectiveness of the assay in pediatric, geriatric, and other special populations (including immunocompromised, pregnant, and diabetic individuals).

Note: "Bio-threat Agents of Interest" for sections 6.6, 6.7, & 6.8 (listed alphabetically): *Bacillus anthracis* (Anthrax), *Botulinum toxin* (Botulism), *Burkholderia mallei* (Glanders) and *Burkholderia pseudomallei* (Melioidosis), Filoviruses (Ebola & Marburg), *Francisella tularensis* (Tularemia), *Rickettsia prowazekii* (Typhus), *Yersinia pestis* (Plague)

Note: Animal samples, if required for these studies, will be provided as Government Furnished Material (GFM).

Antibiotic Resistance Diagnostics for priority bacterial pathogens

6.8 Development, clinical evaluation and FDA clearance/approval of diagnostic tests to detect/identify drug resistant priority public health bacterial pathogens and characterize their resistance profiles, and to support enrollment in clinical trials of new antibiotics.

In accordance with the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) and the Executive Order on Combating Antibiotic Resistant Bacteria, BARDA is expanding the diagnostics program to include targeted funding opportunities in support of advancing innovative rapid and improved diagnostics to detect multi-drug resistant (MDR) priority public health pathogens* and characterize their resistance profiles, both for biological threats and routine healthcare conditions. Priority will be given to:

- tests that are rapid and easy to use at Point of Care (POC) or in a wide-range of laboratory settings,
- tests that are useful for multiple priority public health pathogens* and for at least one bio-threat agents of Interest (see section 6.7 for list),
- proposals that demonstrate a cost sharing commitment by the Offeror.

6.8.1 CLIA waivable, **rapid platforms and assays** for use in POC settings that will be useful to guide targeted therapeutic decisions, **identifying pathogen and resistance or**

susceptibility to relevant antibiotics in a single direct specimen analysis. The assay shall be highly sensitive and specific, and useful for multiple specimen types (e.g., sterile and mixed flora sites). Results should be available in less than 30 minutes.

6.8.2 **Multiplex molecular assays** for use in moderate complexity and high complexity laboratory settings which identify priority bacterial pathogens and genetic determinants of antimicrobial resistance in a single direct specimen analysis. The assays shall be highly sensitive and specific, and useful for multiple specimen types (e.g., sterile and mixed flora sites).

6.8.3 **Tests to enable antibiotic clinical trials** -rapidly rule in/rule out pathogen or interest, and assess resistance profile from clinical specimens. Tests should be designed for use in POC or near patient settings. Results should be available in less than 30 minutes.

6.8.4 Clinically applicable **specimen to result sequencing solutions** with user-friendly simplified workflow and bioinformatics tools appropriate for use in a clinical diagnostics laboratory to identify pathogens with known and novel resistance determinants directly from a broad range of clinical specimen types.

6.8.5 **Novel phenotypic platforms and assays** for use in moderate and high complexity laboratory settings that will shorten the time required to reliably and accurately identify resistance or susceptibility to relevant antibiotics. All results should be available in less than 8 hours. The assays shall be highly sensitive and specific.

6.8.6 CLIA waivable, rapid platforms and assays for use in POC settings that will be useful to reliably distinguish **Viral vs. Bacterial** infections in order to inform appropriate use of antibacterials and antivirals. The assay shall be highly sensitive and specific, and useful for multiple specimen types (e.g., sterile and mixed flora sites). Results should be available in less than 30 minutes.

Note*: Refer to the CDC report "Antibiotic Resistance Threats in the United States, 2013[15]".

Chemical Agent Diagnostics:

Submissions for Chemical Agent Diagnostics will not be considered during the open period of this BAA, unless specifically announced through special instructions. Please monitor future special instructions for specifics on Chemical Agent Diagnostics areas of interest.

Technical Point of Contact for AOI #6: Mr. Rodney Wallace; rodney.wallace@hhs.gov

[15] http://www.cdc.gov/drugresistance/threat-report-2013/index.html

Part II: Research and Technical Objectives

The topics listed below exemplify some of the typical developmental activities in the areas of non-clinical research, manufacturing, clinical evaluation, project management, and regulatory strategy contained in a typical drug, biologic or device development effort. This information is provided to assist and guide Offerors in preparing their Statement of Work (SOW). Offerors shall submit a SOW in their full proposal that addresses these topics as appropriate. Provide as much detail as may be necessary to fully explain the proposed technical approach or method. In the event that an offeror's technical approach provides for performance in excess of one year, the SOW must be presented in a manner so that the base segment and option segments are discrete and non-severable. Each segment must contain specific work elements that must be achieved to support go/no-go milestones that predicate execution of each subsequent option segment of the work.

Consequently, contracts awarded under this BAA may contain contract options that may be unilaterally exercised by the government that either follow or run concurrently with a base period of performance. The length of the base period of the contract is subject to negotiation. Offerors are invited to propose certain discrete stages or areas of work as contract options. Contracts awarded under similar BAAs issued in the past by BARDA for the development of innovative platform technologies have had periods of performance ranging from one to five years, inclusive of options.

For drug and biologic medical countermeasure development efforts, Offerors shall propose a Statement Of Work (SOW) preferred to be consistent with activities between Integrated Technology Readiness Levels (TRLs) 6 to 7 (see https://www.medicalcountermeasures.gov/federal-initiatives/guidance/integrated-trls.aspx) or Attachment 2. For Chemical Radiological and Nuclear (CRN) (Research Areas 4 and 5, Offerors shall propose a SOW that is consistent with activities occurring at TRL 4 or greater (https://www.medicalcountermeasures.gov/federal-initiatives/guidance/integrated- trls.aspx) and should refer to the Areas of Interest (see above) for specific technical guidance. For diagnostics, Offerors shall propose a SOW that is consistent with activities occurring at TRL 4 or greater (see Attachment 1).

Proposal preparation and submission instructions are contained in Part IV.

Small Molecules and Biologics

For Small Molecules and Biologics, the proposed advanced development program should consist of the following elements when applicable:

Elements of an acceptable SOW might include the following sections for the base and each option:

1.1 Program Management
1.2 Non-Clinical Toxicology
1.3 Non-Clinical PK and Efficacy
1.4 Clinical
1.5 Regulatory
1.6 CMC

Applicable elements may be used to organize the description of effort applied to other areas of interest. The following are detailed examples of the types of activities that may be necessary to implement a program:

A. Development Approach:

1. Program Management Representative Activities include but are not limited to:

    a. Identification of and management to, distinct stages of the product development pathway that are gates for Go/No Go decisions for advancing to the next stage of the Integrated Product Development Plan.

    b. Establishment of and tracking of milestones and timelines for the initiation conduct, and completion of product development activities for each stage with a budget (in direct costs) linked to each stage.

    c. Ongoing evaluation of qualitative and quantitative criteria and accompanying data used to assess the scientific merit and technical feasibility of proceeding to the next stage of product development.

    d. Maintaining and managing staff (in-house and contracted) to assure the necessary expertise and dedicated effort to perform the work.

    e. Directing and overseeing subcontractors and consultants to assure successful performance of planned activities within the cost and schedule constraints of the contract.

    f. Conducting performance measurement that shall include establishing an initial plan; defining measurable parameters; defining how these parameters relate to cost and schedule impacts; their approach in providing a detailed schedule that generates a critical path for the project; and a description of the cost- accounting system used or intended to be used based on budget estimates to monitor all costs related to the contract award for both prime- and sub- contractors on a real time bases.

    g. Perform assessments of technical approaches to reduce the Total Life Cycle Cost (TLCC) for the proposed countermeasure throughout the products life cycle and identify strategic approaches to ensure the product has a sustainable commercial value to ensure long term access to the medical countermeasure

2. Non-Clinical Toxicology Research and Development Representative Activities include but are not limited to:

    a. Evaluating the safety, toxicology, pharmacokinetics / pharmacodynamics, bioavailability, solubility, formulation, of the medical countermeasure using both in vitro and animal models following Good Laboratory Practice guidelines (GLP: as defined in the U.S. Code of Federal Regulations - 21CFR Part §58), as and when appropriate.

3. Non-Clinical PK and Efficacy Research and Development Representative Activities include but are not limited to:

a. Screening of small molecule libraries for antitoxin / antimicrobial / antiviral activities (for already approved or licensed product).

b. Evaluating the immunogenicity, efficacy, pharmacokinetics / pharmacodynamics, bioavailability, solubility, formulation, dose, route and schedule of the medical countermeasure using both in vitro and animal models following Good Laboratory Practice guidelines (GLP: as defined in the U.S. Code of Federal Regulations, 21 CFR Part §58), as appropriate.

4. Clinical Evaluation Representative Activities include but are not limited to:

   a. Design and conduct of Phase 1 clinical studies to evaluate the safety and pharmacokinetics of the therapeutic candidate/product in humans in accordance with Good Clinical Practice guidelines (GCP: as defined by 21 CFR §312 and ICH Guidelines document E6.

   b. Design and conduct of a Phase 2 and/or Phase 3 clinical studies in accordance with all Federal regulations and GCP guidelines.

5. Chemistry and Manufacturing Controls (CMC) Representative Activities include but are not limited to:

   a. Development of master and working cell banks under Good Manufacturing Practice guidelines (GMP: as defined in the U.S. Code of Federal Regulations 21 CFR §211).

   b. Process development activities to increase efficiency, yield, quality, and reduce the variability and risk factors in the manufacture of the drug substance and drug product.

   c. Formulation development to evaluate combinations of excipients and their influence on the target product profile and stability.

   d. Manufacture of non-GMP and of GMP pilot lots of candidate product in amounts sufficient to carry out required/proposed non-clinical and Phase 1 and/or Phase 2 clinical trials.

   e. Identification of Critical Quality Attributes (CQA) and Critical Process Parameters.

   f. Manufacturing scale-up plan to lead to consistency lot manufacturing of the candidate product.

   g. Process flow for personnel, material and waste disposal.

   h. Proposed packaging design and execution of fill-finish of final drug product.

   i. Design of stability testing plan and conduct of stability studies on bulk and final product.

   j. Manufacturing/Testing facility plan to support phase I through commercial scale product supply

k. Development of analytical methods and assays appropriate for product characterization and product release, including tests for the identity, purity, potency, and stability of the bulk drug substance and final drug product. Offerors shall identify a stable source and availability of reagents and reference standards for these assays required.

l. Development of Validation Protocol for analytical and assay methods to defining product manufacturing control, performance, potency and product stability indication.

m. Development of processes that would benefit from alternative techniques using CM (e.g. continuous perfusion, continuous synthesis, non column based chromatography), if applicable

n. Integration of continuous mode(s) into manufacturing process and the development of in-line process analytical technologies, if applicable.

o. Continuous processing for homogeneous production of final dosage forms (e.g. tableting, strip film manufacturing system, injection molding, and printing) if applicable.

6. Regulatory Activities include but are not limited to:

a. A clear and comprehensive regulatory master plan that focuses on the crucial pathway integrating all products, risk evaluation and mitigation at all development stages, non-clinical and clinical testing, and manufacturing activities using the most current and available information, including documented and time-relevant consultation with FDA. Plan should include a tentative schedule for regulatory milestones.

b. Establishment and filing of regulatory submissions to the relevant FDA center.

c. Maintenance of a plan for additional studies to support future filing for FDA-approval/clearance.

d. Development of a potential Plan for consideration of an Emergency Use Authorization (EUA) of a medical product (http://www.fda.gov/oc/guidance/emergencyuse.html)

e. Maintaining all required regulatory documentation (investigator brochure, regulatory binder, etc.), providing periodic updates to the FDA as required, and seeking FDA guidance on the conduct of studies that will be used to support approval/licensure/EUA.

f. Conducting site initiation, monitoring, and closeout visits to contract research organizations subcontracted to perform studies.

Diagnostics

For Area of Interest #6 (Diagnostics), the advanced development program should consist of the following elements where applicable:

A. Development Approach:

1. Program Management Representative Activities include but are not limited to:

    a. Identification of, and management to, distinct stages of the product development pathway that are gates for Go/No Go decisions for advancing to the next stage of the Integrated Product Development Plan.

    b. Establishment of and tracking of milestones and timelines for the initiation conduct, and completion of product development activities for each stage with a budget (in direct costs) linked to each stage.

    c. Ongoing evaluation of qualitative and quantitative criteria and accompanying data used to assess the scientific merit and technical feasibility of proceeding to the next stage of product development.

    d. Maintaining and managing staff (in-house and contracted) to assure the necessary expertise and dedicated effort to perform the work.

    e. Directing and overseeing subcontractors and consultants to assure successful performance of planned activities within the cost and schedule constraints of the contract.

    f. Conducting performance measurement that shall include establishing an initial plan; defining measurable parameters; defining how these parameters relate to cost and schedule impacts; their approach in providing a detailed schedule that generates a critical path for the project; and a description of the cost-accounting system used or intended to be used based on budget estimates to monitor all costs related to the contract award for both prime- and sub-contractors on a real time bases.

2. Product Development Representative Activities include but are not limited to:

    a. Perform natural/case history studies of threat agent(s).

    b. Review the pathology of human disease related to threat agent(s)

    c. Identification of biomarkers of disease for threats of interest.

    d. Performance of human or non-GLP animal studies to demonstrate the performance / viability of biomarkers.

    e. Development of assays, reagents, devices, instruments, and consumables, or components thereof, necessary to perform diagnostic tests, either manually or with automated means. This includes the development of tooling and processes necessary to produce these products.

    f. Development of verification and validation protocols and execution of said protocols to prove performance of products developed.

    g. Development of reference standard for use in validation and/or verification.

    h. Development of requirements and design control documents.

i. Production of non-GMP compliant prototypes and reagent lots at laboratory scale.

3. Manufacturing Development Representative Activities include but are not limited to:

   a. Identifying/developing pilot scale manufacturing facilities capable of producing diagnostic systems, assays, reagents, or consumables in compliance with Good Manufacturing Practice guidelines (GMP: as defined in the U.S. Code of Federal Regulations – 21 CFR §211).

   b. Process development activities to increase efficiency, yield, quality, and reduce the variability and risk factors in the manufacture of diagnostic devices, assays, reagents, and consumables.

   c. Manufacture of non-GMP and of GMP pilot lots of candidate product in amounts sufficient to carry out required/proposed integration, validation, verification, animal studies, or clinical trials.

   d. Identification of Critical Quality Attributes (CQA) and Critical Process Parameters.

   e. Manufacturing scale-up plan to lead to consistency lot manufacturing of the candidate product.

   f. Process flow for personnel, material and waste disposal.

   g. Design of stability testing plan and conduct of stability studies assays and reagents.

   h. Develop a risk evaluation and mitigation strategy or similar risk mitigation strategy proposal

   i. Development of procedures and equipment/components for quality acceptance or quality assurance of manufactured products.

   j. Performance of Installation Qualifications (IQ) or Process qualifications (PQ).

   k. Development of manufacturing processes and procedures.

   l. Development of tooling to manufacture products appropriate for pilot scale manufacturing.

4. Clinical Evaluation Representative Activities include but are not limited to:

   a. Design and execution of clinical trials to evaluate the efficacy, safety, sensitivity and specificity of Diagnostic Systems in humans in accordance with Good Clinical Practice guidelines (GCP: as defined by 21 CFR §312 and ICH Guidelines document E6).

5. Regulatory Activities include but are not limited to:

   a. A clear and comprehensive regulatory master plan that includes a strategy for

determination of the appropriate regulatory pathway for the developed diagnostic device. Plan should include a tentative schedule for regulatory milestones.

b. Establishment and filing of regulatory submissions to the correct office with the FDA Center for Devices and Radiological Health (CDRH).

c. Maintenance of a plan for additional studies to support future filing for FDA-approval/clearance.

d. Development of a potential Plan for consideration of an Emergency Use Authorization (EUA) of a medical product (http://www.fda.gov/oc/guidance/emergencyuse.html)

e. Maintaining all required regulatory documentation (investigator brochure, regulatory binder, etc.), providing periodic updates to the FDA as required, and seeking FDA guidance on the conduct of studies that will be used to support approval/licensure/EUA.

f. Conducting site initiation, monitoring, and closeout visits to contract research organizations subcontracted to perform studies.

Part III: Reporting Requirements and Deliverables

Some reports and other deliverables are relevant to specific activities that may or may not be performed during the contract period of performance. The Offeror and the Government will agree during final contract negotiations on which reports and other deliverables are relevant and will be required as deliverables as determined in the negotiated SOW.

As part of the work to be performed under this BAA, the Contractor will prepare and deliver the following reports throughout the period of performance. Each document should be submitted electronically in Microsoft Word, Microsoft Excel, Microsoft Project, and/or Adobe Acrobat PDF file formats.

The following reports are not elements of the Full Proposal submission. They may be required as deliverables during the period of performance of a contract.

Reports:

1. **Technical Progress Reports**
   The frequency of Technical Progress Reporting will be determined by the Government during negotiation of the contract. Typically, on the fifteenth (15) day of each month, the Contractor will submit to the Contracting Officer and the COR a Technical Progress Report describing activities performed during the previous calendar month. The appropriate formats for the Technical Progress Report and Executive Summary will be provided by the COR. The Technical Progress Reports will include project timelines and summaries of product manufacturing, testing, and clinical evaluation activities. A Technical Progress Report will not be required for the month in which the Final Report is due. The Contractor should submit one (1) electronic copy of the Technical Progress Report. Any Technical Progress EVM Report documents should be submitted in Microsoft Word, Microsoft Excel, Microsoft Project, and/or Adobe Acrobat PDF file formats. The Contractor should inform the Contracting Officer and the COR in advance if the delivery of a Technical Progress Report will be delayed.

2. **Final Report**
   By the expiration date of the contract, the Contractor will submit a comprehensive Final Report that details, documents, and summarizes the results of all work performed under the contract. A draft Final Report will be submitted to the Contracting Officer and COR for review and comment, after which the Final Report will be submitted. The Contractor should submit two (2) paper copies and one (1) electronic copy to the Contracting Officer and COR.

There may be additional reports and deliverables required in the final negotiated contract.

Meetings:

The Contractor will participate in regular meetings to coordinate and oversee the contract effort as directed by the Contracting Officer and COR. Such meetings may include, but are not limited to, all Contractors and subcontractors to discuss clinical manufacturing progress, product development, product assay development, scale-up manufacturing development, clinical sample assay development, preclinical/clinical study designs and regulatory issues, or other relevant activities; meetings with individual Contractors and other HHS officials to discuss the technical, regulatory, and ethical aspects of the program; and meeting with Government technical consultants to discuss technical data provided by the Contractor.

Monthly teleconferences between the Contractor and subcontractors and BARDA will be held to review technical progress. BARDA reserves the right to request more frequent teleconferences and face-to-face meetings depending on the nature and importance of the work being performed. The Contractor will receive feedback from BARDA during the monthly teleconference regarding contract performance. The Contractor will have an opportunity to respond and recommend corrective actions.

The only contractual relationship will be between the Government and the prime Contractor. No business obligation exists between the Government and any subcontractors unless a teaming arrangement is established.

Regulatory and Quality Management:

FDA submissions and meetings:

a. The Contractor will forward the dates and times of any meeting with the FDA to BARDA and make arrangements for BARDA staff to attend.

b. The Contractor will provide BARDA the opportunity to review and comment on any documents prior to submission to the FDA. The contractor should provide BARDA with a minimum of five (5) business days to provide comments back to the Contractor.

c. The Contractor will forward the initial draft minutes and final draft minutes of any formal meeting with the FDA to BARDA.

d. The Contractor will provide BARDA with the final draft minutes of any informal meeting with the FDA.

e. The Contractor will forward copies of any relevant Standard Operating Procedures upon request from the Government.

f. The Contractor will provide upon request animal study and/or other data packages developed under this contract. Packages shall include complete protocols and information on critical reagents for animal models developed and/or improved with contract funding.

g. The Contractor will provide upon request raw data and/or specific analysis of data generated with Government funds.

Audits / Site Visits:

FDA Audits

Within thirty (30) calendar days of an FDA audit of Contractor or subcontractor facilities, the Contractor shall provide copies of the audit findings, final report, and a plan for addressing areas of nonconformance to FDA regulations and guidance for GLP, GMP or GCP guidelines as identified in the final audit report.

Other U.S. Government Audits

The Government reserves the right to conduct an audit of the Contractor with 48 hours notice. The Government reserves the right to accompany the Contractor on routine and for-cause site visits and audits of subcontractors. At the discretion of the Government and independent of testing conducted by the Contractor, BARDA reserves the right to conduct site visits and audits and collect samples of product held by the Contractor and subcontractors.

Program Management Plans and Documentation:

1. **Integrated Master Schedule**: An Integrated Master Schedule (IMS), also known by its graphical representation as a Gantt chart, will be submitted by the Offeror as part of their Full Proposal and will be incorporated into the contract. The IMS shall include the key contract progress milestones and Go/No-Go decision criteria. The IMS for the period of performance will be negotiated prior to award.

2. **Integrated Product Development Plan**: Within fourteen (14) calendar days of the effective date of an award, the successful Offeror (or Contractor) shall submit an updated Integrated Product Development Plan (IPDP) which shall be approved by the Contracting Officer's Representative and the Contracting Officer prior to initiation of any activities related to their implementation.

   During the course of contract performance, in response to a need to change the IPDP, the successful Offeror (or Contractor) shall submit a Deviation Report. This plan shall request a change in the agreed-upon Plan and timelines. This plan shall include:

   a. Discussion of the justification/rationale for the proposed change.

   b. Options for addressing the needed changes from the approved timelines, including a cost-benefit analysis of each option.

   c. Recommendations for the preferred option that includes a full analysis and discussion of the effect of the change on the entire product development program, timelines, and budget.

3. **Risk Management Plan**: The Offeror will propose a risk management plan to identify potential risks that may arise during the life of the contract and the impact of these risks on cost, schedule and performance, and appropriate remediation plans. This plan should reference relevant WBS elements where appropriate. The format for such a plan and timeline for submission will be

determined during contract negotiations.

Learn more about ASPR Business Toolkit[16] for additional program management information and templates.

Earned Value Management:

Earned Value Management Systems (EVMS) will be required under contracts in excess of $10M and may be required for contracts in a smaller dollar amount when the contracted work falls within a certain technology readiness level (TRL). Learn more about Tools for Monitoring Development Progress[17].

Offerors will be informed of the need for implementation of an EVMS after at the time of invitation for full proposal or during negotiations. Learn more about AMCG's implementation of Earned Value Management systems[18].

[16] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx
[17] https://www.medicalcountermeasures.gov/federal-initiatives/guidance/about-the-trls.aspx
[18] http://www.phe.gov/about/amcg/contracts/Pages/evm.aspx

Part IV: Special Considerations

Special Instructions will be posted as amendments to the BAA on FedBizOpps when they become apparent. Please monitor this solicitation for future special instructions. In addition, please consider the following:

A. Contractor Responsibility Regarding Sensitive Information:

- The Contractor will investigate violations to determine the cause, extent, loss or compromise of sensitive program information, and corrective actions taken to prevent future violations. The Contracting Officer in coordination with BARDA will determine the severity of the violation. Any contractual actions resulting from the violation will be determined by the Contracting Officer.

B. Security Plan:

- In the event a security plan is needed for this requirement, the Contracting Officer will make a determination and inform the offeror of the need for a security plan. Should a security plan be requested, all pertinent documents for the creation of one will be provided to the offeror by the Contracting Officer.

C. Identification and Disposition of Data:

- The Contractor will be required to provide certain data generated under this contract to the HHS. HHS reserves the right to review any other data determined by HHS to be relevant to this contract. The contractor shall keep copies of all data required by the FDA relevant to this contract for the time specified by the FDA.

D. Confidentiality of Information:

- The following information is covered by HHSAR Clause 352.224-70, Privacy Act (January 2006): Data obtained from human subjects.

E. Publications:

- Any manuscript or scientific meeting abstract containing data generated under this contract must be submitted to BARDA Contracting Officer's Representative for review no less than thirty (30) calendar days for manuscripts and fifteen (15) calendar days for abstracts before submission for public presentation or publication. Contract support shall be acknowledged in all such publications. A "publication" is defined as an issue of printed material offered for distribution or any communication or oral presentation of information.

F. Press Releases:

- The Contractor agrees to accurately and factually represent the work

conducted under this contract in all press releases. Misrepresenting contract results or releasing information that is injurious to the integrity of the Government may be construed as improper conduct. Press releases shall be considered to include the public release of information to any medium, excluding peer-reviewed scientific publications. The contractor shall ensure that the Contracting Officer's Representative has received an advance copy of any press release related to this contract not less than four (4) working days prior to the issuance of the press release.

G. Export control notification:

- Offerors are responsible for ensuring compliance with all export control laws and regulations that maybe applicable to the export of and foreign access to their proposed technologies. Offerors may consult with the Department of State with any questions regarding the International Traffic in Arms Regulation (ITAR) (22 CRF Parts 120-130) and /or the Department of Commerce regarding the Export Administration Regulations (15 CRF Parts 730-774).

H. Manufacturing Standards:

- The Good Manufacturing Practice Regulations (GMP)(21 CFR Parts 210-211) and regulations pertaining to biological products (21 CFR Part 600) and regulations pertaining to diagnostic products (21 CFR Part 860) will be the standard to be applied for manufacturing, processing, packagin storage and delivery of this product.

- If at any time during the life of the contract, the Contractor fails to comply with GMP in the manufacturing, processing, packaging, storage, stability and other testing of the manufactured drug substance or product and delivery of this product and such failure results in a material adverse effect on the safety, purity or potency of the product (a material failure) as identified by the FDA, the Offeror shall have thirty (30) calendar days from the time such material failure is identified to cure such material failure. If the Offeror fails to take such an action to the satisfaction of the USG Contracting Officer's Representative within the thirty (30) calendar day period, then the contract may be terminated.

I. Prohibition on contractor Involvement with Terrorist Activities:

- The Contractor acknowledges that U.S. Executive Orders and Laws, including but not limited to Executive Order 13224 and Public Law 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under this contract.

J. Invoices:

- The Contracting Officer and Contractor will discuss the Contract Type

during contract negotiations. Regardless of contract type, a successful contractor should expect requirements similar to the following invoicing requirements:

1. The contractor agrees to provide a detailed breakdown on invoices of the categories similar, but not limited to, the following:

    a. Direct Labor - List individuals by name, title/position, hourly/annual rate, level of effort, and amount claimed.

    b. Fringe Benefits - Cite rate and amount

    c. Overhead - Cite rate and amount

    d. Materials & Supplies - Include detailed breakdown when total amount is over $1,000.

    e. Travel - Identify travelers, dates, destination, purpose of trip, and amount. Cite COA, if appropriate. List separately, domestic travel, general scientific meeting travel, and foreign travel.

    f. Consultant Fees - Identify individuals and amounts.

    g. Subcontracts - Attach subcontractor invoice(s).

    h. Equipment - Cite authorization and amount.

    i. G&A - Cite rate and amount. j. Total Cost

    j. Fixed Fee

    k. Total CPFF (if applicable)

2. Monthly invoices must include the cumulative total expenses to date, adjusted (as applicable) to show any amounts suspended by the Government. In order to verify allowability, further breakdown of costs may be requested at the Government's discretion.

3. The contractor agrees to immediately notify the Contracting Officer in writing if there is an anticipated overrun (any amount) or unexpended balance (greater than 10 percent) of the amount allotted to the contract, and the reasons for the variance. Also refer to the requirements of the Limitation of Cost (FAR 52.232-20) clause in the contract..

Part V: Quad Chart/White Paper Instructions (Stage 1)

The application process is in two stages as follows:

- **Quad Chart/White Paper (Stage 1)**
- Full Proposal (Stage 2)
    - Volume I - Technical Proposal
    - Volume I – Technical Proposal Attachments
    - Volume II - Cost Proposal
    - Volume II – Cost Proposal Attachments

Quad Chart and White Paper Preparation

Interested Offerors shall submit a Quad Chart, and White Paper which expands on the information provided in the Quad Chart. The initial submission is limited to a cover page, one-page Quad Chart, White Paper not to exceed ten (10) pages, and an addendum (not to exceed two (2) pages) as discussed below. **This results in a submission packet not to exceed 14 pages.** If submissions exceed these limitations, only those pages previously defined will be reviewed.

Combine all files and forms into a single searchable PDF file before submitting.

Complete a cover sheet, Quad Chart, White Paper and a Rough Order of Magnitude (ROM) estimate of costs must be submitted in accordance with the preparation guidance below. The Quad Chart and White Paper should describe the effort in sufficient detail to allow evaluation of the concept's technical merit and its potential contribution to the BARDA mission. Offerors whose Quad Chart and White Paper receive a favorable evaluation will be invited to submit a Full Proposal [Stage 2]. Offerors whose Quad Chart and White Paper did not receive a favorable evaluation will be notified by email. Note that an offeror who receives an unfavorable rating is not precluded from a submitting a Full Proposal, however, it is strongly recommended the offeror resubmit a revised white paper.

As a white paper is not considered a "proposal," no debriefing will be provided defined by FAR Subpart 15.5.

Quad Chart Format: The format, information and sample template is located in Attachment #5. All Quad Charts should be laid out in landscape format.

1. Heading: Title, BAA#, Research Area of Interest, Technical/Administrative point of contact (Name, Email, Phone), Company's Name & Address
2. Upper left: Objective, description of effort
3. Lower left: Benefits of proposed technology, challenges, maturity of technology research area addressed as indicated by the TRL (see Attachment 1)

4. Upper right: Picture or graphic

5. Lower Right: Milestones, period of performance, Rough Order of Magnitude (ROM) cost estimate.

White Paper Format

1. The white paper should provide a brief technical discussion of the offeror's objective, approach, level of effort, and the nature and extent of the anticipated results. Specifically, the white paper should include, at a minimum, the following core elements:

   a. A brief discussion on how the proposed countermeasure aligns with the objectives of the PHEMCE Implementation Plan and the BAA area of interest to which the submission is responding.

   b. Sufficient data to justify the proposed Technology Readiness Level (TRL) maturity of the candidate product or device. Appropriate supporting information could include summary data from preclinical studies and clinical trials, process development and manufacturing milestones, and regulatory status.

   c. A clear and concise plan for meeting product development objectives that includes all key activities (e.g., non-clinical, clinical, manufacturing, and regulatory activities).

   d. A high-level Gantt chart showing an overview of the proposed activities and timelines.

   e. A brief description of the offeror's intellectual property ownership of the proposed countermeasure. If intellectual property impediments may affect the Offeror's ability to develop the proposed technology, Offerors should briefly outline their strategy for addressing such impediments.

   f. An overview of the offeror's capabilities and experience (past and current) as they relate to the proposed development activities.

2. The cost portion of the White Paper shall contain a brief cost estimate revealing all the component parts of the proposal.

3. As an addendum to the White Paper, include biographical sketches (two pages) of the key personnel who will perform the research or managing project activities, highlighting their relevant qualifications and experience.

4. Any applicable references should also be cited if they are relevant to the proposed workplan.

5. Restrictive markings on White Papers: Proposal submissions will be protected from unauthorized disclosure in accordance with FAR Subpart 15.207, applicable law and HHS regulations. Offerors that include data in their proposal which they do not want disclosed shall mark their proposal in accordance with the instructions contained in HHSAR 352.215-1(e): Restrictions on disclosure and use of data. **Please note that any white paper submitted under this solicitation may be shared with other**

government agencies for non-BARDA funding considerations and evaluation.

6. IMPORTANT NOTE: The Government may reject white paper submissions that are deemed non-compliant. Non-compliant is defined in this context as a white paper which significantly deviates from the instructions in this BAA.

7. Furthermore, White Papers which are outside the scope of the BAA on their face may be returned to the Offeror.

ROM Preparation:

A Rough Order of Magnitude cost estimate (ROM cost estimate) is required with the Quad Chart and White Paper submission. The ROM cost estimate is based on the top level task(s) or objective(s) set forth in the white paper. It uses a top down estimating approach based on expert knowledge and/or previous experience. For the white paper each task (or objective) needs to have a ROM cost estimate with it. A total ROM cost (i.e. sum of all the tasks or objectives) should also be provided.

Quad Chart and White Paper Submission

Quad Chart and White Papers WILL NOT BE ACCEPTED after 4:30 PM (Eastern Standard Time) on 31 October 2017.

White Papers must be emailed directly to the following email address:

FLU-BAA@HHS.GOV.

IMPORTANT: The subject line of the email should read **BAA-16-100-SOL-00002 QUAD CHART & WHITE PAPER for Research Area #** .". White Papers do not require any special forms, but must be submitted in the following format:

- Single PDF formatted file as an email attachment
- Page Size: 8 ½ x 11" with 1" Margins
- Spacing – single
- Font – Arial, 11 point

The file will not exceed 10 Megabytes of storage space. Movie and sound file attachments, URL Links, or other additional files, will not be accepted.

Classification: All Quad Chart and White Paper submissions must be UNCLASSIFIED.

Chart and White Paper Review

Quad Chart and White Paper submissions will be reviewed by a panel with primary focus on the submission's technical merit and relevance to BARDA programmatic priorities. Offerors will receive a response within 90 calendar days of the next interim or final deadline following submission. Technical feedback will be provided in the response, and the response will express whether a Full Proposal is recommended or not. Offerors may receive a response sooner than 90 calendar days depending on the number of White

Papers submitted to BARDA. Offerors who submit white papers after a given submission deadline may not have their materials reviewed until after the next submission date. **Debriefings prescribed under FAR Part 15 for Quad Chart and White Paper will not be provided, however, technical feedback will be provided in the response letter from BARDA.**

IMPORTANT NOTE: Titles given to the White Papers and Full Proposals should be descriptive of the work proposed and not be merely a copy of the title of this solicitation.

Part VI: Full Proposal Instructions (Stage 2)

The application process is in two stages as follows:

- Quad Chart/White Paper (Stage 1**)**
- **Full Proposal (Stage 2)**
    - Volume I - Technical Proposal
    - Volume I – Technical Proposal Attachments
    - Volume II - Cost Proposal
    - Volume II – Cost Proposal Attachments

Stage 2: Full Proposal Instructions

With a successful review of the Offeror's White Paper, the Offeror will be invited to submit a full proposal. Offerors invited to submit a Full Proposal are advised to schedule a teleconference with technical and contracting staff to address the written administrative and technical clarifications contained in the invitation for Full Proposal. The Full Proposal must be prepared in two separate Volumes as follows: Volume I Technical Proposal and Volume II Cost Proposal. Each Volume will have its separate related Attachments. Additional applicable forms will be provided in the letter of invitation to submit a full proposal.

Volume I – Technical Proposal

The technical proposal page limit is 50 pages of technical volume (excluding items A-C) and 70 pages of appended material *unless otherwise specified* in the invitation letter, including figures, tables and graphs**. This results in a Technical Proposal package not to exceed 120 pages.** If the proposal exceeds the number of pages specified, only the pages up to the limit will be reviewed. A page is defined as 8.5 X 11 inches, single-spaced, with one-inch margins in type not smaller than 11 point font. This should include the following items:

A. Cover Page:

- The follow information shall be provided on the first page of the technical proposal:

1. The words "Volume I: Technical Proposal"
2. BAA number
3. Title of proposal (descriptive of the work proposed and not a copy of the title of the solicitation)
4. Research Area of Interest
5. Date of submission

6. Prime Offeror and complete list of subcontractors, if applicable

7. Technical contact (name, address, phone/fax, electronic mail address)

8. Administrative/business contact (name, address, phone/fax, electronic mail address)

9. Proposed period of performance

B. Official Transmittal Letter:

- This is an official transmittal letter including:

1. The name, title, mailing address, telephone number, and fax number of the company or organization;

2. The name, title, mailing address, telephone number, fax number, and e-mail address of the division point of contact regarding decisions made with respect to the Offeror and who can obligate the proposal contractually;

3. The name, title, mailing address, telephone number, fax number, and e-mail address and those individual(s) authorized to negotiate with the USG; and

4. A statement indicating you are submitting a final Full Proposal for consideration.

C. Table of contents:

- An alphabetical/numerical listing of the sections within the proposal, including corresponding page numbers.

D. Executive Summary**:**

- An abstract or synopsis of the proposed project. The Government recommends that the length of the summary remain within 1 to 2 pages.

E. Introduction:

- Provide a brief description (one to two paragraphs) of the overall project and objectives in broad terms that indicates the size and magnitude of the proposed effort.

F. Statement of Work:

- **[NOTE TO OFFEROR: The Technical Requirements shall begin with the following introductory paragraph.]** "Independently, and not as an agent of the Government, the Contractor shall furnish all necessary services, qualified professional, technical, and administrative personnel, material, equipment and facilities, not otherwise provided by the Government under the terms of this contract, as needed to perform the tasks set forth below."

- The SOW should clearly detail the scope and objectives of the effort and the technical approach. It is anticipated that the proposed SOW will be incorporated as

an attachment to the resultant award instrument. To that end, the proposal should be specific, non-severable, discrete work segments, and be written as a self-standing document without any proprietary restrictions. The SOW should include a detailed listing of the technical tasks/subtasks organized by discrete work periods (base and option periods) including appropriate Work Breakdown Structure references for each task.

G. Development Approach**:**

- A detailed description of the experimental design, including the rationale for experimental approaches, acceptance criteria and measurable objectives, and a description of alternative approaches to be employed if these methods do not achieve the defined goals. Previous results and data should be included as necessary to justify the proposed development activities.

H. Gantt Chart/Integrated Master Schedule (IMS), Work Breakdown Structure (WBS) and Contract Go/No-Go Milestones:

- A detailed Gantt Chart/IMS with associated WBS and Contract Go/No – Go Milestones for each phase (base and options) will be provided as part of the technical submission. The break points of different phases proposed in the contract should be indicated. Learn more about the ASPR Business Toolkit[19] for additional program management information and templates.

I. Deliverables:

- A detailed description of the results and products to be delivered inclusive of the timeframe in which they will be delivered.

J. Key Personnel:

- A listing of key personnel (including proposed consultants) who possess the necessary education, training, and experience to successfully perform the work identified in the technical proposal (resumes to be included in the Appended material). A summary of related activities should also be provided for key personnel; instructions are provided in Attachment 4.

K. Organizational Chart:

- An organizational chart for the project with affiliations (who will report to whom).

L. Contractor provided Facilities, Infrastructure and other Resources Representative Activities.

- If applicable or specifically requested by the government this may include but is not limited to:

1. Current facility design including quality control labs for testing & release, laboratory areas supporting formulation and assay development, manufacturing process flow,

[19] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx

and animal studies.

2. Major equipment and layout (e.g. preliminary piping and instrumentation drawing).

3. Manufacturing capacity expansion plans to match the proposed manufacturing scale up.

4. Overview of the management of Quality Systems at the facility.

5. List of capabilities for clinical activities conducted in house and at contract research organizations. List of clinical sites engaged for product evaluations.

6. Qualified animal facilities where GLP studies would be conducted and appropriate certifications for humane care and use of vertebrate animals.

7. The handling, storing and shipping of potentially dangerous biological and chemical agents, including Select Agents, under biosafety levels required for working with the biological agents under study.

8. Validation master plan for key equipment, analytical methods and manufacturing process.

9. Commercial capabilities of the Offeror, including current products, and marketing, distribution and customer support capabilities (as applicable)

10. List of key vendors or service providers, locations, and brief description of their expertise/experience.

M. BARDA Intramural Core Services:

- Offerors are hereby informed that BARDA maintains a comprehensive set of medical countermeasure product development core services and manufacturing technology capabilities [e.g. Centers for Innovation in Advanced Development and Manufacturing (CIADM), Nonclinical Development Network (NDN)]. Offerors may be given the opportunity to utilize these core services and are encouraged to evaluate their potential application in their proposed work plan. Learn more about BARDA Core Services[20].

N. Past Performance Information:

- The Offeror shall provide a list of the last three (3) Government contracts during the past three years and all contracts currently being performed that are similar in nature to the proposed project. Contracts listed may include those entered into by the Federal Government, agencies of state and local Governments and commercial concerns. Offerors may also submit past performance information regarding predecessor companies, key personnel who have relevant experience or subcontractors that will perform major or critical aspects of the requirement when such information is relevant to the instant acquisition. For the purposes of this BAA, a "major subcontract" is defined as a subcontract that exceeds $25,000.

[20] https://www.medicalcountermeasures.gov/barda/core-services/

- Include the following information for each contract or subcontract listed:

    1. Name of Contracting Organization

    2. Contract Number (for subcontracts, provide the prime contract number and the subcontract number)

    3. Contract Type

    4. Total Contract Value

    5. Description of Requirement

    6. Contracting Officer's Name and Telephone Number

    7. Program Manager's Name and Telephone Number

    8. North American Industry Classification System Code

- The Offeror may provide information on problems encountered on the identified contracts and the Offeror's corrective actions.

O. Additional Requirements:

The offeror must also represent that they have adequately addressed the following requirements:

1. Research involving Human Subjects/Anatomical Substances (if proposed).

2. Research involving Animals (if proposed).

3. Evidence of GLP Compliance (if appropriate).

4. Evidence of GMP Compliance (if appropriate).

5. Evidence of GCP Compliance (if appropriate).

6. Evidence of Laboratory Licensure Requirements (if appropriate)

7. Compliant Use of Select Agents (if appropriate)

8. All required representations and certifications are completed and on file.

P. Deviation Report:

During the course of contract performance, in response to a need to change the SOW or IPDP, the Offeror shall submit a Deviation Report. This report shall request a change in the agreed-upon Plan and timelines. This report shall include:

1. Discussion of the justification/rationale for the proposed change.

2. Options for addressing the needed changes from the approved timelines, including a cost-benefit analysis of each option.

3. Recommendations for the preferred option that includes a full analysis and discussion of the effect of the change on the entire product development program, timelines, and budget

Q. Prior Approval Notification:

- The Offeror shall carry out activities within the contract SOW only as requested and approved by the Contracting Officer, and may not conduct work on the contract without prior approval from the Contracting Officer, including initiating work that deviates from the agreed-upon IPDP.

Volume I - Technical Proposal Attachments

Attachments should contain supplemental data that accompanies the technical proposal. The combined page total of Attachments in Volume I will be specified in the full proposal invitation letter. Additional specific information to be included is referenced below. If a particular item in not relevant to the proposed effort, state that it is not applicable along with any supporting justification. See Special Considerations Section for additional information on any of the Items listed below.

Table 2: Technical Proposal Attachments

	Item	Required	Reference & Document Type
1	Updated Quad Chart	Yes	Template in Attachment #5. Please note any differences with the original Quad Chart.
2	Protection of Human Subjects	If Applicable	Human Subject Research (45 CFR 46)[21]
3	Animal Welfare	If Applicable	Office of laboratory Animal Welfare (OLAW)[22]
4	Intellectual Property	Yes	
5	Biographical Sketches	Yes	
6	Use of Select Agents	If Applicable	Federal Select Agent Program[23] Agriculture Select Agent Service[24]
7	Laboratory License Requirements	If Applicable	
8	Target Product Profile (TPP)	Yes	Template in Attachment #2

[21] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
[22] http://grants.nih.gov/grants/olaw/olaw.htm
[23] http://www.selectagents.gov/
[24] www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth/sa_import_into_us/sa_ag_select_agent

	Item	Required	Reference & Document Type
9	Supporting Data	No	Any additional product development data referenced in Volume I may be included here, provided that the Attachments remain within the page limit.

1. Quad Chart

- Offerrors will need to include a revised Quad Chart showing differences from the original Quad Chart submitted during Stage 1 - Quad Chart/White Paper.

2. Protection of Human Subjects

- All research under this BAA must address the involvement of human subjects and protections from research risk related to their participation in the proposed research plan and comply with 32 CFR 219, 10 U.S.C. 980, and, as applicable, 21 CFR Parts 11, 50, 54, 56, 312)(45 CFR Part 46) and the ICH as well as other applicable federal and state regulations. HHS Policy also requires that women and members of minority groups and their subpopulations: children and the elderly (pediatric and geriatric) must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification is provided with respect to the health of the subjects or the purpose of the research. Learn more about HHS policy on studies that involved human subjects[25].

- Research projects involving humans and/or human specimens can only be initiated with written approval by the BARDA Project Officer.

- The Good Clinical Practice Regulations (GCP)(21 CFR Parts 50, 54, 56 312)(45 CFR Part 46)(ICH E6) as well as other applicable federal and state regulations will be standards that apply for use of human subject and/or human specimens in clinical studies.

- If at any time during the life of the contract, the Contractor fails to comply with GCP as identified by regulations outline above , the Offeror shall have thirty (30) calendar days from the time such material failure is identified to cure such or initiate cure to the satisfaction of the USG Project Officer. If the Offeror fails to take such an action within the thirty (30) calendar day period, then the contract may be terminated.

3. Animal Welfare

- If the Offeror proposes to use contract funds to conduct animal studies, the Offeror must demonstrate its understanding and ability to comply with the Public Health Services (PHS) Policy on Humane Care and Use of Laboratory Animals http://grants.nih.gov/grants/olaw/olaw.htm). If the Offeror has an Animal Welfare Assurance on file with the Office of Extramural Research (OER), Office of Laboratory Animal Welfare (OLAW), provide the Assurance number with the

[25] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

proposal. If the Offeror proposes animal studies, the Offeror must submit a plan that describes how the Offeror will comply with the PHS Policy and addresses the five points listed below:

a. Provide a detailed description of the proposed use of the animals in the work outlined in the experimental design and methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.

b. Justify the use of animals, the choice of species, and the numbers used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and their numbers.

c. Provide information on the veterinary care of the animals involved.

d. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices where appropriate to minimize comfort, distress, pain, and injury.

e. Describe any euthanasia method to be used and the reasons for its selection.

f. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations. Learn more about AVMA Guidelines for the Euthanasia of Animals[26].

4. Intellectual Property

- Offerors must describe any limitations on any intellectual property (patents, inventions, trade secrets, copyrights, technical data, or trademarks) that will impact the Offeror's performance of the contract or impact the Government's subsequent use of any deliverable under the contract. Offerors must describe how the Government can accomplish the stated objectives of this BAA with the limitations described or proposed by the Offeror. Offerors must include this information in Volume I – Attachments.

- For issued patents or published patent applications that will be used in the performance of the contract, provide the patent number or patent application publication number, a summary of the patent or invention title, and indicate whether the Offeror is the patent or invention owner. If the Offeror is licensing the candidate drug for the proposed work, Offeror is required to provide copies of any licensing agreements, or portions thereof, applicable to the candidate drug before a potential contract can be entered into.

5. Biographical Sketches

- This Section shall contain the biographical sketches for only the key personnel from both the contractor and subcontractor(s): The Full Proposal must list the

[26] https://www.avma.org/KB/Policies/Pages/Euthanasia-Guidelines.aspx

names and proposed duties of the professional personnel, consultants, and key subcontractor employees assigned to the project. Their resumes should be included in the attachments in Volume I of the Full Proposal. The resumes should contain information on education, background, recent experience, and specific or technical accomplishments as they pertain to their ability to support the objectives of this project. The approximate percentage of time each individual will be available for this project must be stated. The proposed staff hours of each individual should be allocated against each project task or subtask.

- Offerors must also include a list of those individuals authorized to contractually obligate the entity, as well as a list of those individuals authorized to negotiate with the Government on behalf of the entity.

6. Use of Select Agents

- An HHS chaired committee of contracting, security, safety and scientific program management will assess the applicability of the facilities, regulations, policies, and procedures for meeting the U.S. requirements described in 42 CFR part 73, 7 CFR part 331, and/or 9 CFR part 121.

7. Laboratory License Requirements

- The Contractor shall comply with all applicable requirements of Section 353 of the Public Health Service Act (Clinical Laboratory Improvement Act as amended). This requirement shall also be included in any subcontract for services under the contract.

8. Target Product Profile (TPP)

- Offerors should use the template in Attachment #2 to develop the Target Product Profile (TPP) to discuss the TPP of proposed candidate medical countermeasures.

a. The intended use or indication of the proposed medical countermeasure.

b. The intended product profile (strength, quality, purity and identity) noting the performance specifications and features of the medical countermeasure that provide benefit.

c. A description of the medical countermeasure as it is currently configured.

d. A description of the manufacturing process including expected formulation (configuration) of the final product.

e. A description and developmental status of the assays for product release which provide characterization, strength, identity, and purity, as well as any needed assays for product activity and efficacy.

f. Discussions with appropriate FDA reviewers that is relevant to development activities for the proposed medical countermeasure, including plans for generating data to support an Investigational New Drug (IND), Biologics License Application (BLA) or New Drug Application (NDA), Pre-Market Approval and/or

510(k) application: summary of any prior, time-relevant communication with FDA relevant to the product development for the indication noted; summary of audits and inspections relative to the current development or proposed manufacturing (Including at key sub-contractors) of the intended product.

9. Supporting Data

- Any additional product development data referenced in Volume I may be included here, provided that the Attachments remain within the page limit.

Volume II – Cost Proposal

The cost proposal shall contain sufficient information for meaningful evaluation, and should not exceed the page limitation specified in the full proposal invitation letter. Additionally, a cost summary (not to exceed 2 pages) must be prepared and submitted in conjunction with the detailed cost proposal. The detailed costs must readily track back to the cost presented in the summary and the WBS, IMS, and SOW. The Offeror must also provide a narrative to support the requirements in each cost element. The cost breakdown by tasks should reference the WBS task in the Technical Proposal. SOW Options should be priced separately.

A. Cover Page:

- The following information shall be provided on the first page of the cost proposal:

    1. The words "Volume II: Cost Proposal";
    2. BAA Number;
    3. Title of proposal (descriptive of the work proposed and not a copy of the title of the solicitation):
    4. Research Area of Interest:
    5. Prime Offeror (name, address, telephone number, and email address);
    6. Technical contact (name, telephone number, email address);
    7. Administrative contact (name, address, telephone number, and email address) (if available);
    8. Audit Office (name, address, telephone number, and email address) (if available);
    9. Proposed cost and/or price; profit or fee (as applicable); and total;
    10. The following statement: "By submitting this proposal, the Offeror, if selected for discussions, grants the Contracting Officer or an authorized representative the right to examine, at any time before award, any of those books, records, documents, or other records directly pertinent to the information requested or submitted."
    11. Date of submission; and
    12. Authorized representative (name, title and signature).
    13. DUNS number and CAGE code.

- This cover sheet information is for use by Offerors to submit information to the Government when cost or pricing data are not required but information to help establish price reasonableness or cost realism is necessary. Such information is not considered cost or pricing data, and shall not be certified in accordance with FAR 15.406-2.

B. Basic Cost/Price Information:

- The final cost proposal with a full cost proposal shall contain sufficient information to allow the Government to perform a basic analysis of the proposed cost or price of the work. This information shall include the amounts of the line items of the proposed cost or price. These elements will include the following elements by milestone event and/or proposed period as applicable:

    1. Direct Labor- Individual labor category or person, with associated labor hours and unburdened direct labor rates;

    2. Indirect Costs – Fringe Benefits, Overhead, G&A, etc. (Must show base amount and rate) Offerors should submit a copy of their most recent indirect cost rate agreement negotiated with any federal audit agency, if applicable.;

    3. Travel – Separate by destinations and include number of trips, durations - number of days, number of travelers, per diem (hotel and meals in accordance with the Federal Travel Regulations), airfare, car rental, if additional miscellaneous expense is included, list description and estimated amount, etc;

    4. Subcontract – A cost proposal shall be submitted by each subcontractor proposed under the contract. The subcontractor's cost proposal should include on company letterhead the following:

        a. Complete company name and mailing address, technical and administrative/business point of contacts, email

        b. Address, and telephone number.

        c. Include the DUNS number and CAGE code.

        d. A commitment letter from the proposed subcontractor's business official that includes:

            1) Willingness to perform as a subcontractor for specific duties (list duties) or a Statement of Work

            2) Proposed period of performance

            3) Supporting documentation for proposed costs (personnel documents to verify salaries, vendor quotes for equipment, negotiated indirect cost rate agreement; and

            4) Quotes from two other potential subcontractors for similar services (see FAR 44.202(a)(5)

        If the subcontractor's work entails any unpredictable aspects (e.g. includes experimentation, process development, etc.) a cost proposal conforming to all requirements of this section shall be provided, and shall reference the WBS of the prime contractor's proposal.

        If the subcontractor/vendor is providing commercially available, routine

services/products (e.g. facilities audits; manufacturing from a defined protocol; off-the-shelf reagents, hardware, or software; etc.) then a less detailed price quote is allowable. In each case where the latter level of detail is provided, the Offeror should assign subcontractor/vendor costs to the WBS, and should be prepared to document multiple competitive quotes for the service/product.

5. Consultants – For consultant subcontract arrangement, provide draft consulting agreement or other document which verifies the proposed loaded daily/hourly rate and labor category;

    a. Written verification from the consultant of their proposed rate, along with a statement that it is their usual and customary rate charged to other customers;

    b. Description of the work to be performed by the consultant and direct relevance to the contract work. Include information on why this expertise is not available in-house; and

    c. Verification that costs for the consultant are available within the total estimate cost of the contract and 4)Quotes from two other consultants for similar services (see FAR 44.202(a)(5)

6. Materials should be specifically itemized with costs or estimated costs. Where the cost is greater than $3,000, indicate pricing method (e.g., competition, historical costs, market survey, etc.). Include supporting documentation, i.e. vendor quotes, catalog price lists and past invoices of similar purchases.

7. Other Direct Costs, especially any proposed items of equipment. Equipment generally must be furnished by the Offeror. Justifications must be provided when Government funding for such items is sought.

8. Fee/profit including percentages.

C. Salary Rate Limitation:

- Pursuant to current and applicable prior HHS appropriations acts, it is anticipated that offerors submitting full proposals under this BAA may be subject to a salary rate limitation on funds used to pay the direct salary of individuals. The applicability of this mandate will be confirmed at the time a full proposal is requested and is subject to the appropriations used to fund the effort.

    1. Congress has stipulated in the HHS appropriations act that, under applicable extramural contracts appropriated funds cannot be used to pay the direct salary of an individual at a rate in excess of the Federal Executive Schedule Level II.

    2. For purposes of the salary rate limitation, the terms ``direct salary,'' ``salary'', and ``institutional base salary'', have the same meaning and are collectively referred to as ``direct salary'', in this clause. An individual's direct salary is the annual compensation that the Contractor pays for an individual's direct effort (costs) under the contract. Direct salary excludes any income that an individual may be permitted to earn outside of duties to the Contractor. Direct salary also excludes fringe benefits, overhead, and general and

administrative expenses (also referred to as indirect costs or facilities and administrative [F&A] costs). Note: The salary rate limitation does not restrict the salary that an organization may pay an individual working under an HHS contract or order; it merely limits the portion of that salary that may be paid with Federal funds.

3. The salary rate limitation also applies to individuals under subcontracts.

4. See the salaries and wages pay tables on the U.S. Office of Personnel Management Web site for Federal Executive Schedule salary levels that apply to the current and prior periods.

D. Travel

- Identify as separate items and provide uniform cost assumptions for each travel requirement, e.g., contract initiation meeting, annual progress review meetings, periodic meetings with the Contracting Officer's Representative, travel associated with training requirements and clinical site monitoring visits. Include the number of trips per year, location, number of days, and the number of Contractor/subcontract staff, as well as any external advisory group members for who travel expenses will be provided by the Contractor.

Volume II - Cost Proposal Attachments

Attachments to Volume II contain supplemental data of a cost and non-cost nature that should accompany the cost proposal. The combined total of all attachments should not exceed the page limitation specified in the full proposal invitation letter. Additional specific information to be included is referenced below. If a particular item in not relevant to the proposed effort, state that it is not applicable along with any supporting justification.

Table 3: Cost Proposal Attachments

	Item	Required	Reference & Document Type
1	DUNS, TIN, CAGE, and NAICS	Yes	Full Proposal Volume II – Cost Proposal
2	Representations and Certifications	Yes	System for Award Management[27] (SAM)
3	Breakdown of Proposed Estimated Cost (Plus Fee) and Labor Hours	Yes	Part VIII: Attachment #7 ASPR Business Toolkit[28] (for template)
4	SF-424 (for grant)	If applicable	Required: SF-424, SF-424A, SF-424B, SF-LLL For grant: Additional resources and templates are available in the ASPR Business Toolkit[29] and Grants.Gov[30]
5	HHS Small Business Subcontracting Plan	If applicable	Small Business SubContracting Plan[31]
6	Summary of Related Activities	Yes	Part VIII: Attachment #4 (for template)
7	Lobbying Activities	Yes	For Grant: SF-LLL: Disclosure of Lobbying Activities[32] For Contract: HHSAR 352.203-70[33]
8	Report of Government-Owned, Contractor-Held Property	If applicable	ASPR Business Toolkit[34] (for template)
9	Financial Capacity and Annual Financial Report	Yes	

[27] https://www.sam.gov/
[28] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx
[29] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx
[30] http://www.grants.gov/web/grants/forms.html
[31] http://www.hhs.gov/asfr/ogapa/osbdu/smallbusiness/subcontractplan.html
[32] https://www.whitehouse.gov/sites/default/files/omb/grants/sflllin.pdf
[33] http://www.hhs.gov/grants/contracts/contract-policies-regulations/hhsar/subpart352/
[34] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx

	Item	Required	Reference & Document Type
10	Past Performance Contact Information	Yes	Part VI, Section 10
11	Total Life Cycle Costs (TLCC) estimate for the proposed product or technology	Yes	Part VIII: Attachment #8, TLCC Definition. Additional resources and templates are available in the AMCG Business Toolkit[35].

1. **DUNS[36], TIN, CAGE, and NAICS[37]**

   - These identification numbers or codes are required for companies to work with the government.

2. **Representations and Certifications**

   - In accordance with FAR 4.1201 prospective Offerors shall complete and update the annual representations and certifications at System for Award Management (SAM). Learn more about System for Award Management[38] (SAM) for completion of annual Representations and Certifications.

3. **Breakdown of Proposed Estimated Cost (Plus Fee) and Labor Hours**

   - Complete the template to provide a breakdown of the proposed estimated cost (plus fee) and labor hours.

4. **SF-424**

   - The SF-424, SF-424A, SF-424B, and SF-LLL forms are required to be completed for grants and cooperative agreements. Refer to the letter of invitation to submit a full proposal for additional details and form requirements.

5. **HHS Small Business Subcontracting Plan**

   - Successful contract proposals that exceed $700,000, submitted by all but small business concerns, will be required to submit a Small Business Subcontracting Plan in accordance with FAR 19.704.

6. **Summary of Related Activities**

   - This specific information must be provided by the Offeror pertaining to the Project Director, Principal Investigator, and each of any other proposed key professional individuals designated for performance under any resulting contract.

[35] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx
[36] http://www.dnb.com/
[37] http://www.census.gov/eos/www/naics/index.html
[38] https://www.sam.gov/

7. Lobbying Activities

- In accordance with Prohibition on the Use of Appropriated Funds for Lobbying Activities [HHSAR 352.203-7], the following clause shall be inserted: "Pursuant to the current HHS annual appropriations act, except for normal and recognized executive-legislative relationships, the Contractor shall not use any HHS contract funds for (i) publicity or propaganda purposes; (ii) the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself; or (iii) payment of salary or expenses of the Contractor, or any agent acting for the Contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

8. Report of Government-Owned, Contractor-Held Property

- Complete the spreadsheet available at the ASPR Business Tookit[39], if Government Furnished Property (GFP) is a part of the proposal. Additionally, include a business case justification for review that outlines that providing GFP is in the Government's best interest and that there is no other commercial alternative other than GFP. Additionally, justify how any proposed costs of GFP are "fair and reasonable". Include the completed spreadsheet with your cost proposal.

9. Financial Capacity & Annual Financial Report:

- The offeror shall indicate if it has the necessary financial capacity, working capital, and other resources to perform the contract without assistance from any outside source. If not, indicate the amount required and the anticipated source. The offeror may also be asked to submit a copy of the organization's most recent annual report in the cost proposal attachment.

10. Past Performance:

- The Offeror shall provide a list of the last three (3) Government contracts during the past three years and all contracts currently being performed that are similar in nature to the BAA scope. Contracts listed may include those entered into by the Federal Government, agencies of state and local governments and commercial concerns. Offerors may also submit past performance information regarding predecessor companies, key personnel who have relevant experience or subcontractors that will perform major or critical aspects of the requirement when such information is relevant to the instant acquisition. For the purposes of this BAA, a "major subcontract" is defined as a subcontract that exceeds the simplified acquisition threshold.

- Include the following information for each contract or subcontract listed:

    1. Name of Contracting Organization

[39] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx

2. Contract Number (for subcontracts, provide the prime contract number and the subcontract number)
3. Contract Type
4. Total Contract Value
5. Description of Requirement
6. Contracting Officer's Name and Telephone Number
7. Program Manager's Name and Telephone Number
8. North American Industry Classification System Code

- The Offeror may provide information on problems encountered on the identified contracts and the Offeror's corrective actions.

11. Total Life Cycle Cost

- An increasing emphasis is being placed on the management of costs thorough out the operational life cycle of awards to be made under this BAA. Consequently, the TLCC spreadsheet available in the ASPR Business Toolkit should be completed. In addition, provide any additional information that best describes and forecasts the total costs of your proposal throughout its projected operational life cycle. These costs should include any one-time setup expenses, ongoing sustainment costs and potential decommissioning or disposal costs associated with your proposal. Include this information with your cost proposal.

Stage 2: Full Proposal Submission

Full proposals will be accepted under this BAA for 6 months following the final white paper submission date.

Unless directed by the Contracting Officer otherwise, mail two (2) copy of the Full Proposal to the below address. Additionally, Offeror should submit an electronic copy via email, to an email address to be provided in the invitation letter.* Note: Additional copies may be requested in the Full Proposal Invitation Letter.

Contracting Officer

Office of Acquisitions Management, Contracts and Grants 330 Independence Ave,

S.W. Room G644

Washington, D.C. 20201

Offeror shall include in the Full Proposal Cover Sheet:

- The name, title, mailing address, telephone number, and fax number of the company or organization;
- The name, title, mailing address, telephone number, fax number, and e-mail address of the division point of contact regarding decisions made with respect to the the Offeror and who can obligate the proposal contractually;
- The name, title, mailing address, telephone number, fax number, and e-mail address and those individual(s) authorized to negotiate with the USG; and
- A statement indicating you are submitting a final Full Proposal for consideration.

Submission file format for the electronic copy: Each volume of the proposal must be submitted as a separate and searchable Portable Document File (PDF) compatible with Adobe Acrobat version 9.0 or earlier. Each individual file shall not exceed 10 megabytes of storage space.

Notification to Offerors: All Offerors will receive an email acknowledging receipt of their Quad Chart/White Paper and Full Proposal.

Information to be requested from Offerors: Offerors whose proposals are selected for potential award may be contacted to provide additional clarification and technical information if required for award.

Offerors that are not responsive in a timely manner to Government requests for information (defined as meeting Government deadlines established and communicated with the request) may be removed from award consideration. Offerors that request significant revisions to their proposal subsequent to their selection for potential award may be removed from award consideration. Offerors may also be removed from award consideration if the Offeror and the Government fail to negotiate mutually agreeable terms within a reasonable period of time.

Part VII: Quad Chart/White Paper and Full Proposal Evaluation

A. Quad Chart/White Paper and Full Proposal Evaluation Criteria

The selection of one or more sources for award will be based on an evaluation of each Full Proposal. Full Proposals will be evaluated by a Peer or Scientific Review process and will be evaluated based on the following criteria that are listed in descending order of importance. The sub-criteria listed under a particular criterion are of equal importance to each other. Pursuant to FAR 35.016(e), the primary basis for selecting proposals for acceptance shall be technical, importance to agency programs, and fund availability. Therefore, when together non-cost related evaluation criteria significantly outweigh cost-related evaluation criteria.

1. Program relevance

    a. Medical countermeasures that align with the projected near or mid-term objectives identified in the PHEMCE Implementation Plan for CBRN Threats https://www.medicalcountermeasures.gov/Reports.aspx), and with the priorities described in the applicable research area of interest (Part I).

    b. Medical countermeasures that focus on diagnosis, post-event prophylaxis, post-exposure treatment/mitigation, and are also effective when administered within the treatment window for that agent.

    c. Medical countermeasures that are readily administered during a public health emergency. For instance, oral, self administration is preferred over intra-muscular (i.m.) or subcutaneous (s.c.) injection, and i.m. or s.c. injection is preferred over intravenous administration from a logistical and emergency response perspective. Medical countermeasures whose developmental maturity preferably aligns with TRLs 6 to 7 for Drugs and Biologics (TRL 4 and 5 for CRN; see https://www.medicalcountermeasures.gov/federal-initiatives/guidance/integrated-trls.aspx) or TRL 4 or greater for Diagnostics (see Attachment 1)

    d. Medical Countermeasures that are suitable for use with pediatric and other special populations.

    e. The extent to which the proposed effort fills an unmet programmatic need.

2. Overall scientific and technical merits of the proposal

    a. The degree of innovation and potential to offer a revolutionary increase in capability or a significant reduction in cost commensurate with the potential risks of the innovative approach.

    b. The soundness, feasibility, and validity of the proposed plans, methods, techniques, and procedures of the technical proposal.

    c. The Offeror's understanding of the scope of the proposed work and the technical effort needed to complete it.

    d. The reasonableness of the proposed schedule.

e. The Offeror's understanding of the statutory and regulatory requirements for FDA licensure/approval status of proposed work.

f. Ownership of Intellectual Property.

g. The degree of development of the technology and its readiness for the marketplace.

h. The Offeror has proposed a product with 1) a sustainable commercial value to ensure long term access to the medical countermeasure 2) a feasible technical approach that optimizes the product in a way that reduces the Total Life Cycle Cost (TLCC) for the proposed countermeasure throughout the products life cycle.

3. Offeror's capabilities and related experience, including the qualifications, capabilities, and experiences of the proposed key personneld

    a. The expertise of technical personnel proposed.

    b. The Offeror's experience in relevant efforts with similar resources.

    c. The reasonableness of the proposed project management approach and expertise of the project management personnel proposed.

    d. The necessary facilities and infrastructure to carry out the proposed effort. (The Offeror may identify specific subcontractors and other partners).

B. Other Evaluation Factors and Considerations

In accordance with FAR 35.016 (e), the primary basis for selecting proposals for acceptance shall be technical, importance to agency programs, and fund availability. Cost realism and reasonableness shall also be considered to the extent appropriate.

1. Cost/Price

Each price / cost response will be reviewed for price / cost realism, reasonableness, and overall best value to the government. Proposals will be reviewed to determine if the costs proposed are based on realistic assumptions, reflect a sufficient understanding of the technical goals and the objectives of the BAA and are consistent with the Offeror's technical approach. For proposals with a likelihood of commercial application, cost-sharing may be positively evaluated under this criterion.

2. Past Performance

Past performance information will be evaluated to the extent of determining the Offeror's ability to perform the contract successfully. Offerors shall submit the following information as part of their proposal.

The Government is not required to contact all references provided by the Offeror. Also, references other than those identified by the Offeror may be contacted by the Government to obtain additional information that will be used in the evaluation of the

Offeror's past performance.

The Government will use the Past Performance Information Retrieval System (PPIRS) to help assess Offeror past performance.

3. Subcontracting Program Evaluation

For contract awards to be made to large businesses, the socio-economic merits of each proposal will be evaluated, but not scored, based on the extent of the Offeror's commitment in providing meaningful subcontracting opportunities for small businesses, small disadvantaged businesses, woman-owned businesses, service disabled veteran- owned small businesses, Hub-zone small business concerns, historically black colleges and universities, and minority institutions.

4. U.S.-based Job Preference

For Offerors providing U.S. based jobs in the technical and/or administrative activities needed to accomplish milestone activities associated with product development will be afforded if the assessment on other criteria is equal.

5. Requested Proof of Concept Studies

Full Proposals which were requested to provide Proof of Concept (POC) studies will be evaluated in regard to the POC design, power of the studies, budget, and timelines. If the technical evaluation does not result in a favorable decision, the Offeror may be asked to perform additional work on the product's development at their cost and resubmit. A successful review of the POC design will result in a negotiation for a contract to perform the POC (or a negotiated POC) as a base contract with or without Options, all subject to availability of funds.

The final evaluation will be based on an assessment of the overall best value to the government based on these criteria. Awards, if any, will be made based on proposal evaluation and funds availability.

C. Evaluation Rating

The Full Proposal will be evaluated and categorized as follows:

Acceptable: The proposal has been evaluated and deemed appropriate for additional consideration and discussion. The proposal is generally considered well-conceived, scientifically, and technically sound and important to program goals and objectives. Proposal submissions given this designation may proceed into negotiations. This rating does not guarantee contract award; will consider program priorities, negotiations, and is subject to the availability of funds.

Unacceptable: The proposal has been evaluated and deemed inappropriate for additional consideration and discussion at this time. Proposals given this designation are not technically sound or do not meet program priorities and will be rejected.

D. Additional Information

Offerors selected for negotiations may be subject to inspections of their facilities and Quality Assurance/Quality Control (QA/QC) capabilities. The decision to inspect specific facilities will be made by the Contracting Officer in coordination with the Contracting Officer's Representative. If inspections are performed during the negotiations, the results of the inspection will be considered in final selection for award of a contract. Offerors, including proposed subcontractors, will be requested to make all non-proprietary records, including previous regulatory inspection records, and staff available in response to a pre-award site visit or audit by BARDA or its designee. Pre- award site visits may be made with short notice. Offerors are expected to guarantee the availability of key staff or other staff determined by the Government as essential for purposes of this site visit.

Offerors are hereby notified that the Government intends to use a Technical Evaluation Panel (TEP), in determining which initiatives should be funded. The TEP may consist of Government personnel and technical contract support personnel.

All personnel assigned to a TEP have signed a Nondisclosure Agreement, Conflict of Interest Disclosure, and will be made aware that proposals shall not be duplicated, used, or disclosed in whole or in part for any purpose other than to evaluate the proposal. Any offeror who states in writing that they are unwilling to allow contractor members of the TEP to review their proposal shall have their proposal returned without evaluation.

Offerors whose full proposals are issued an "Unacceptable" letter and are not invited to negotiations may request a debriefing (10 U.S.C. 2305(b)(6)(A) and 41 U.S.C. 3705). (1) The offeror may request a preaward debriefing by submitting a written request for debriefing to the contracting officer within 3 days after receipt of the notice of exclusion from negotiations. At the offeror's request, this debriefing may be delayed until after award. If the debriefing is delayed until after award, it shall include all information normally provided in a postaward debriefing. Debriefings delayed pursuant to this paragraph could affect the timeliness of any protest filed subsequent to the debriefing. If the offeror does not submit a timely request, the offeror need not be given either a preaward or a postaward debriefing. Offerors are entitled to no more than one.

Part VIII: Attachments

Attachment 1: Technology Readiness Level Criteria

Minimum Technology Readiness Level (TRL) criteria have been identified for each Research Areas of Interest. Offerors must identify in their Quad Chart and White Paper that such criteria have been met for the proposed medical countermeasure product. Two different Technology Readiness Level (TRL) criteria are provided here.

Attachment 1A: Diagnostics and Medical Devices TRLs adapted from Q-TRLs

This document contains Diagnostics TRL's taken from the Diagnostics Q-TRLs developed and approved by the PHEMCE Diagnostics IPT.

Table 4: Technical Readiness Level and Description for Diagnostics and Medical Devices

TRL Level	TRL Description
1	**Review of Scientific Knowledge.** Active monitoring of scientific knowledge base to identify clinical pathological markers for diagnostic countermeasure candidates. Scientific findings are reviewed and assessed as a foundation for characterizing approaches to intervene in disease. Basic research needs identified.
2	**Concept Generation and Development of Experimental Designs** Develop research plans to answer specific questions and experimental designs for addressing the related scientific issues and to establish feasibility. Focus on practical applications based on basic principles.
3	**Characterization of Preliminary Candidates(s) and Feasibility Demonstration** Begin R&D, data collection, and analysis in order to verify feasibility. Explore alternative concepts, identify and evaluate critical technologies and components, and begin characterizing specifications required. Demonstrate the performance of candidate diagnostic targets and high risk components. Develop a business case for the proposed product.
4	**Optimization and Preparation for Assay, Component, and Instrument Development** Prepare for test system development. Finalize diagnostic target(s) and methods for detecting or quantitating target(s). Develop detailed plans and finalize critical design requirements. Execute commercial agreements with key external development partners. Identify manufacturing resources, vendor sourcing, and experimental designs
5	**Product Development – Reagents, components, subsystems and modules** Develop reagents and buffers. Build and test non-GLP prototypes of components and subsystems. Code and unit test software. Begin pilot scale manufacturing preparations. Develop protocols for assay and integration testing Initiate reagent stability testing. Hold pre-IDE meeting with FDA. Initiate Design History file.
6	**System integration & testing** Integrate and test alpha and beta instruments/devices, software and assays, evaluating performance and updating specifications. Implement design improvements to address defects discovered during testing. Produce and evaluate pilot lots of reagents and beta (pilot) instruments. Increase the maturity of software. Prepare for clinical testing. Complete short term stability testing of reagents.
7	**Analytical Verification and Preparation for Clinical Studies** Evaluate assay and integrated diagnostic system performance utilizing contrived, retrospective human and animal samples. Make preparations for clinical evaluation. Begin preparation for full scale production of instruments and assays.
8	**Clinical Studies and/or evaluation with Animal Studies, FDA Clearance or Approval, Finalize GMP manufacturing preparations.** Complete clinical evaluations. Prepare and submit FDA filing. **End of TRL8:** Acquire FDA approval, or clearance.
9	**Post-Clearance / Post-Approval Activities** Perform post market surveillance, field studies in designated sites; monitor performance, reliability, fitness for use. Establish and maintain appropriate Quality Systems compliant manufacturing capability/inventory. Deliver USG ordered product if applicable

Attachment 1B: Technology Readiness Level (TRL) Definitions for Medical Countermeasure Products (Drugs and Biologics)[40,41]

These TRL criteria can also be found at:
MedicalCountermeasures.GOV

NOTE: *When using these criteria, a medical countermeasure product should be rated at a particular level only after the sponsor has completed all activities listed in that level (e.g., a product is rated at TRL 4 once it completes all of the activities listed in TRL 4).*

Table 5: Technical Readiness Level and Description for Drugs and Biologics

Level	Description
TRL 1	**Review of Scientific Knowledge Base** Active monitoring of scientific knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies.
TRL 2	**Development of Hypotheses and Experimental Designs** Scientific "paper studies" to generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues. Focus on practical applications based on basic principles observed. Use of computer simulation or other virtual platforms to test hypotheses.
TRL 3	**Target/Candidate Identification and Characterization of Preliminary Candidate(s)** Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components, and begin characterization of candidate(s). Preliminary efficacy demonstrated *in vivo*. **3A** Identify target and/or candidate. **3B** Demonstrate *in vitro* activity of candidate(s) to counteract the effects of the threat agent. **3C** Generate preliminary *in vivo* proof-of-concept efficacy data (non-GLP (Good Laboratory Practice)).

[40] This document is designed for evaluating the maturity of medical countermeasure development programs. For a detailed description of development processes for assays and animal models, please consult the Technology Readiness Levels for Product Development Tools (PDTs), developed by the PDT Working Group of the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) and available at: http://www.medicalcountermeasures.gov

[41] This document does not serve as official FDA Guidance nor does it represent FDA's current thinking on this topic. For the purposes of a regulatory application seeking licensure or approval for a specific medical product, additional data may be required by FDA.

Level	Description
TRL 4	**Candidate Optimization and Non-GLP In Vivo Demonstration of Activity and Efficacy** Integration of critical technologies for candidate development. Initiation of animal model development. Non-GLP *in vivo* toxicity and efficacy demonstration in accordance with the product's intended use. Initiation of experiments to identify markers, correlates of protection, assays, and endpoints for further non-clinical and clinical studies. **Animal Models:** Initiate development of appropriate and relevant animal model(s) for the desired indications. **Assays**: Initiate development of appropriate and relevant assays and associated reagents for the desired indications. **Manufacturing:** Manufacture laboratory-scale (i.e. non-GMP (Good Manufacturing Practice)) quantities of bulk product and proposed formulated product. **4A** Demonstrate non-GLP *in vivo* activity and potential for efficacy consistent with the product's intended use (i.e. dose, schedule, duration, route of administration, and route of threat agent challenge). **4B** Conduct initial non-GLP toxicity studies and determine pharmacodynamics and pharmacokinetics and/or immune response in appropriate animal models (as applicable). **4C** Initiate experiments to determine assays, parameters, surrogate markers, correlates of protection, and endpoints to be used during non-clinical and clinical studies to further evaluate and characterize candidate(s).
TRL 5	**Advanced Characterization of Candidate and Initiation of GMP Process Development** Continue non-GLP *in vivo* studies, and animal model and assay development. Establish draft Target Product Profiles. Develop a scalable and reproducible manufacturing process amenable to GMP. **Animal Models:** Continue development of animal models for efficacy and dose-ranging studies. **Assays:** Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate. **Manufacturing:** Initiate process development for small-scale manufacturing amenable to GMP. **Target Product Profile:** Draft preliminary Target Product Profile. Questions of shelf life, storage conditions, and packaging should be considered to ensure that anticipated use of the product is consistent with the intended use for which approval will be sought from FDA. **5A** Demonstrate acceptable Absorption, Distribution, Metabolism and Elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing. **5B** Continue establishing correlates of protection, endpoints, and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose once clinical data are obtained.

Level	Description
TRL 6	**GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s)** Manufacture GMP-compliant pilot lots. Prepare and submit Investigational New Drug (IND) package to FDA and conduct Phase 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article. **Animal Models:** Continue animal model development via toxicology, pharmacology, and immunogenicity studies. **Assays:** Qualify assays for manufacturing quality control and immunogenicity, if applicable. **Manufacturing:** Manufacture, release and conduct stability testing of GMP-compliant bulk and formulated product in support of the IND and clinical trial(s). **Target Product Profile:** Update Target Product Profile as appropriate. **6A** Conduct GLP non-clinical studies for toxicology, pharmacology, and immunogenicity as appropriate. **6B** Prepare and submit full IND package to FDA to support initial clinical trial(s). **6C** Complete Phase 1 clinical trial(s) that establish an initial safety, pharmacokinetics and immunogenicity assessment as appropriate.
TRL 7	**Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)**[42] Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate.[43] Conduct Phase 2 clinical trial(s).[42] **Animal Models:** Refine animal model development in preparation for pivotal GLP animal efficacy studies. **Assays:** Validate assays for manufacturing quality control and immunogenicity if applicable. **Manufacturing:** Scale-up and validate GMP manufacturing process at a scale compatible with USG requirements. Begin stability studies of the GMP product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production. **Target Product Profile:** Update Target Product Profile as appropriate. **7A** Conduct GLP animal efficacy studies as appropriate for the product at this stage.[43]

[42] Identification of later regulatory stages of clinical development in this document (e.g., Phase 2, Phase 3) may not apply to some products being developed under the "Animal Rule". Other than human safety studies, no additional clinical data may be feasible or ethical to obtain. For additional information on the "Animal Rule", please see: http://www.fda.gov/OHRMS/DOCKETS/98fr/053102a.htm

[43] These could include GLP animal efficacy studies required by FDA at this stage in support of an Emergency Use Authorization (EUA). The scientific evidence required for issuance of an EUA will be handled on a case-by-case basis and will depend on, among other things, the nature and extent of the threat at any point during the product development timeline, from the initiation of Phase 1 studies through licensure or approval. GLP animal efficacy study requirements may also vary by product type (e.g., vaccine, therapeutic, prophylactic) and U.S. government agency program office.

Level	Description
	7B Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2).[42]
TRL 8	**Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials[42], and FDA Approval or Licensure** Finalize GMP manufacturing process. Complete pivotal animal efficacy studies or clinical trials (e.g., Phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit NDA/BLA. **Manufacturing:** Complete validation and manufacturing of consistency lots at a scale compatible with USG requirements. Complete stability studies in support of label expiry dating. **Target Product Profile:** Finalize Target Product Profile in preparation for FDA approval. **8A** Complete pivotal GLP animal efficacy studies or pivotal clinical trials (e.g., Phase 3), and any additional expanded clinical safety trials as appropriate for the product.[42] **8B** Prepare and submit New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA. **8C** Obtain FDA approval or licensure.
TRL 9	**Post-Licensure and Post-Approval Activities** **9A** Commence post-licensure/post-approval and Phase 4 studies (post-marketing commitments), such as safety surveillance, studies to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate.[44] **9B** Maintain manufacturing capability as appropriate.

[44] For products approved under the "Animal Rule", confirmatory efficacy data are required, if such studies are feasible and ethical, and may be obtained from use during an event.

Attachment 2: Target Product Profile Template

The success of a product development program requires a relentless focus on the desired characteristics of the resulting medical countermeasure product. During Stage 2, in addition to the Full Proposal, Offerors are requested to provide a Target Product Profile. The template immediately below is as a tool for Offerors to describe the objectives of their advanced research and development activities, and to update dynamically as supporting data about their product is obtained. All Offerors are encouraged to submit a Target Product Profile for the proposed medical countermeasure, with a particular focus on elements 1-4. For those products for which the Target Product Profile format is not applicable, appropriate equivalent information regarding the development objectives should be provided.

Target Product Profile Template
Target Product Profile: ***Drug Name***
(may be modified for use with devices)

Table 6: Target Product Profile: Drug Name

Milestone (meeting or submission)	Date	*TPP Submitted? Y/N	TPP Version Date	TPP Discussed? Y/N
Pre-IND				
IND Submission				
EOP1				
EOP2A				
EOP2/Pre-Phase 3				
Pre-NDA/BLA				
Other (specify)				
Pre-IDE				
IDE Submission				
510(k) or PMA				
Other (specify)				

1 Indications and Usage

Target	Annotations
A statement that the drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, OR *A statement that the drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, OR* *A statement that the drug is indicated for the relief of symptoms associated with a disease or syndrome, OR* *A statement that the drug is indicated for a particular indication only in conjunction with a primary mode of therapy*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date* *When listing studies, consider:* *The intent to develop evidence to support safety and efficacy in selected subgroups (i.e., limitations of use)* *Tests needed for selection or monitoring of patients (i.e., susceptibility tests)* *Whether safety considerations require the drug to be reserved for certain situations (i.e., in refractory patients)* *Whether the drug is to be used on a chronic basis* *What evidence will be developed to support comparator statements regarding safety or effectiveness*

Comments:

2 Dosage and Administration

Target	Annotations
For each indication, state the following: *Route of administration* *Recommended usual dose* *Dose range shown to be safe and effective* *Exposure (dose- or blood level-response relationship, if any)* *Dosage intervals or titration schedule* *Usual duration of treatment course when treatment is not chronic* *Dosage adjustments (e.g., in specific genotypes, pediatric patients, geriatric patients, or patients with renal or hepatic disease)* *Tests for guiding dosing (e.g., target plasma drug levels, therapeutic range, response biomarkers)*	*Summary information regarding completed or planned studies to support the safety and effectiveness of the proposed dosage and route of administration:* *Protocol #, Serial #, Submission date*

Comments:

3 Dosage Forms and Strengths

Target	Annotations
Include information on the available dosage forms, including strength or potency of dosage	*Summary information regarding completed or planned studies to support the dosage forms*

form in metric system and a description of identifying characteristics of dosage forms	*and strengths:* *Protocol #, Serial #, Submission date*

Comments:

4 Contraindications

Target	**Annotations**
List situations in which the drug might be contraindicated, including: *Increased risk of harm because of age, sex, concomitant therapy, disease state* *Adverse reactions which would limit use* *Known, not theoretical, hazards*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date* *Or, literature references describing contraindication for drug class.*
Comments:	

5 Warnings and Precautions

Target	**Annotations**
Include a description of clinically significant adverse reactions and potential safety hazards and limitations of use because of safety considerations, as reasonable evidence of these issues is established or suspected during the drug development program. A causal relationship need not be demonstrated. *Include information regarding any special care to be exercised for safe use, including precautions that are not required under any other section of the label.* *Identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions.*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date* *Or, literature references describing significant adverse reactions shared by the drug class of the new drug.*
Comments:	

6 Adverse Reactions

Target	**Annotations**
Describe overall adverse reaction profile of the drug based on entire safety database. List adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. Within a listing, adverse reactions should be categorized by body system, severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions should be listed in decreasing order of frequency.	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date*

Include the studies in the development program that will address adverse reactions associated with a particular drug class.	

Comments:

7 Drug Interactions

Target	Annotations
Describe clinically significant interactions, either observed or predicted (i.e., other prescription drugs or over-the-counter drugs, class of drugs, or foods such as grapefruit juice or dietary supplements); practical advice on how to prevent drug-drug interactions; (description of results from studies conducted or observations from the integrated safety summary); drug-laboratory test interactions (known interference of drug with lab test outcome).	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

8 Use in Specific Populations

Target	Annotations
Consider the following: *Limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the population.*	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date* *If there are no plans to study the drug in a specific population, include rationale.*

Comments:

8.1 Pregnancy *(This subsection can be omitted if the drug is not absorbed systemically)**:***
Teratogenic effects: Pregnancy Categories: A, B, C, D, X
Non-teratogenic effects: Other effects on reproduction, the fetus, or newborn.

8.2 Labor and Delivery: *Use during labor or delivery, effects on mother, fetus, duration of labor, delivery, and effects on later growth of newborn.*

8.3 Nursing Mothers: *If the drug is absorbed systemically, information about excretion of drug in human milk and effects on the nursing infant. Describe pertinent adverse events in animal offspring or tumorigenicity potential if it is detected or suspected.*

8.4 Pediatric Use: *Statements relevant to the use of the drug product in the pediatric population (birth to 16 years of age). Cite any limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the pediatric population.*

8.5 Geriatric Use: *Statements relevant to the use of the drug product in the geriatric population (age 65 and older). Cite any limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the referenced population.*

8.6 Additional Subsections: *Use of drug in other specified populations (e.g., those with renal or hepatic impairment).*

9 Drug Abuse and Dependence

Target	Annotations
Include the following subsections, as appropriate for the drug:	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

9.1 Controlled Substance: *Anticipated DEA schedule.*
9.2 Abuse: *Identify types of abuse and adverse reactions pertinent to them. Identify particularly susceptible patient populations.*
9.3 Dependence**:** *Discuss potential for dependence and describe the characteristic effects resulting from psychological or physical dependence.*

10 Overdosage

Target	Annotations
Provide specific information about: *Signs, symptoms, and lab findings associated with an overdosage of the drug* *Complications that can occur with overdose of the drug (e.g., organ toxicity)* *Concentrations of the drug in biofluids associated with toxicity or death* *The amount of the drug in a single overdose that is ordinarily associated with symptoms, and the amount of the drug in a single overdose that is likely to be life-threatening* *Whether the drug is dialyzable* *Recommended general treatment procedures*	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date* *Update with human data, if available.*
Comments:	

11 Description

Target	Annotations
Include the proprietary name and established name, dosage form and route of administration, qualitative and quantitative ingredients, pharmacologic or therapeutic class, and any other important physical and chemical characteristics.	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

12 Clinical Pharmacology

Target	Annotations
Include a concise factual summary of the clinical pharmacology and actions of the drug in humans. Data that describe the drug's pharmacologic activity can be included in this section, including biochemical or physiological mechanism of action, pharmacokinetic information, degree of absorption, pathway for biotransformation, percent dose unchanged, metabolites, rate of half-lives including elimination concentration in body fluids at therapeutic and toxic levels, degree of binding to plasma, degree of uptake by a particular organ or fetus, and passage across the blood-brain barrier. Include the following subsections:	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date* *If applicable, a subsection (e.g., 12.4 Microbiology) can be created under this section heading and all of the microbiology information for antimicrobial products consolidated into that subsection.*
Comments:	

12.1 Mechanism of Action: *Summarize **established** mechanisms of action in humans at various levels (e.g., receptor membrane, tissue, organ, whole body). Do not include theorized mechanisms of action.*

12.2 Pharmacodynamics: *Include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect or those related to adverse effects or toxicity. Include data on exposure-response relationship and time course of pharmacodynamic response.*

12.3 Pharmacokinetics: *Describe clinically significant pharmacokinetics of a drug or active metabolites (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Include results of pharmacokinetic studies that establish the absence of an effect, including pertinent human studies and in vitro data.*

13 Nonclinical Toxicology

Target	Annotations
Include the following subsections, as appropriate:	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*
Comments:	

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Results of long-term carcinogenicity studies — species identified

Mutagenesis results

Reproduction study results

13.2 Animal Toxicology and/or Pharmacology: *Ordinarily, significant animal data necessary for safe and effective use of the drug in humans should be included in other sections of the labeling, as appropriate. If the pertinent animal data cannot be appropriately incorporated into*

other sections of the labeling, this subsection can be used.

14 Clinical Studies

Target	Annotations
Provide a description of studies that support statements about the efficacy or safety benefits. Consider including a description of supporting tables and graphs.	*Summary information about completed or planned studies regarding the intent to develop evidence to support benefits of treatment (i.e., safety or efficacy benefits of primary or secondary endpoints in the selected population):* *Protocol #, Serial #, Submission date* *Measurement instruments (e.g., patient-reported outcomes instrument) and references to supporting development and validation documentation* *Also consider including where the studies will be (or have been) run (i.e., geographical area).*
Comments:	

15 References — *Can include when labeling must summarize or otherwise rely on recommendation by authoritative scientific body, or a standardized methodology, scale, or technique, because information is necessary for safe and effective use.*

16 How Supplied/Storage and Handling

Target	Annotations
Include information about the available dosage forms to which the labeling will apply and for which the manufacturer or distributor will be responsible. For example: *Strength of the dosage form* *Units in which the dosage form ordinarily is available* *Information to facilitate identification of dosage forms* *Special handling and storage conditions*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date*
Comments:	

17 Patient Counseling Information

Target	Annotations
Include information for prescribers to convey to patients to use the drug safely and effectively. For example: *Precautions concerning driving* *Concomitant use of other substances that may have harmful additive effects* *Proper use and disposal of syringes and needles* *Adverse reactions reasonably associated with use of the drug* *Lab tests and monitoring required* *Indicate whether a Patient Package Insert or MedGuide are planned.*	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*
Comments:	

1. This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
2. For the purposes of this guidance, all references to *drug* include both human drugs and therapeutic biological products unless otherwise noted. All references to another product including *in vitro diagnostic* and other devices.
3. We update guidance periodically. To make sure you have the most recent version of a guidance, check the following web pages at:
   - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm
   - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm.
   - http://www.fda.gov/MedicalDevices/default.htm
4. See the guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*
5. A clean copy of the Target Product Profile Template can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf
6. Critical Path Initiative: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm

Attachment 3: Regulatory Guidance for Devices

Overview of Device Regulation[45]

Introduction

FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

- Radiation-emitting Electronic Products

Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. A description of device classification and a link to the Product Classification Database is available at "Classification of Medical Devices."

The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:

- Establishment registration,
- Medical Device Listing,
- Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA),
- Investigational Device Exemption (IDE) for clinical studies
- Quality System (QS) regulation,
- Labeling requirements, and
- Medical Device Reporting (MDR)

Establishment Registration - 21 CFR Part 807

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA. All registration information must be verified annually between October 1st and December 31st of each year. In addition to registration, foreign manufacturers must also designate a U.S. Agent. Beginning October 1, 2007, most establishments are required to pay an establishment registration fee.

- Establishment Registration

[45] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm

- U.S. Agents

Medical Device Listing - 21CFR Part 807

Manufacturers must list their devices with the FDA. Establishments required to list their devices include:

- manufacturers,
- contract manufacturers that commecially distribute the device,
- contract sterilizers that commercially distribute the device,
- repackagers and relabelers,
- specification developers,
- reprocessors single-use devices,
- remanufacturer
- manufacturers of accessories and components sold directly to the end user
- U.S. manufacturers of "export only" devices
- Medical Device Listing

Premarket Notification 510(k) - 21 CFR Part 807 Subpart E

If your device requires the submission of a Premarket Notification 510(k), you cannot commercially distribute the device until you receive a letter of substantial equivalence from FDA authorizing you to do so. A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent.

- Premarket Notification 510(k)

On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 became law. It authorizes FDA to charge a fee for medical device Premarket Notifcation 510(k) reviews. A small business may pay a reduced fee. The application fee applies to Traditional, Abbreviated, and Special 510(k)s. The payment of a premarket review fee is not related in any way to FDA's final decision on a submission.

- 510(k) Review Fees

Most Class I devices and some Class II devices are exempt from the Premarket Notification 510(k) submission. A list of exempt devices is located at:

- 510(k) Exempt Devices

If you plan to send a 510(k) application to FDA for a Class I or Class II device, you may find 510(k) review by an Accredited Persons beneficial. FDA accredited 12 organizations

to conduct a primary review of 670 types of devices. By law, FDA must issue a final determination within 30 days after receiving a recommendation from an Accredited Person. Please note that 510(k) review by an Accredited Person is exempt from any FDA fee; however, the third-party may charge a fee for its review.

- Third Party Review

Premarket Approval (PMA) - 21 CFR Part 814

Product requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device.

- Premarket Approval

Beginning fiscal year 2003 (October 1, 2002 through September 30, 2003), medical device user fees apply to original PMAs and certain types of PMA supplements. Small businesses are eligible for reduced or waived fees.

- PMA Review Fees

Investigational Device Exemption (IDE) - 21CFR Part 812

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA. Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of nonsignificant risk must be approved by the IRB only before the study can begin.

Investigational Device Exemption

Quality System Regulation (QS)/Good Manufacturing Practices (GMP) - 21 CFR Part 820

The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.

- Quality System

Labeling - 21 CFR Part 801

Labeling includes labels on the device as well as descriptive and informational literature that accompanies the device.

- Labeling

Medical Device Reporting - 21 CFR Part 803

Incidents in which a device may have caused or contributed to a death or serious injury must to be reported to FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported. The MDR regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner.

- Medical Device Reporting

Attachment 4: Summary of Related Activities

The following specific information must be provided by the Offeror pertaining to the Project Director, Principal Investigator, and each of any other proposed key professional individuals designated for performance under any resulting contract.

During negotiations, the Offeror has a continuing obligation to update the Government regarding changes to the information provided below.

a. Identify the total amount of all presently active federal contracts/cooperative agreements/grants and commercial agreements citing the committed levels of effort for those projects for each of the key individuals***** in this proposal.

Professional's Name and Title/Position:

Identifying Number	Agency	Total Effort Committed
1.		
2.		
3.		
4.		

*****If an individual has no obligation(s), so state.

b. Provide the total number of outstanding proposals, exclusive of the instant proposal, having been submitted by your organization, not presently accepted but in an anticipatory stage, which will commit levels of effort by the proposed professional individuals*****.

Professional's Name and Title/Position:

Identifying Number	Agency	Total Effort Committed
1.		
2.		
3.		
4.		

*****If no commitment of effort is intended, so state.

c. Provide a statement of the level of effort to be dedicated to any resultant contract awarded to your organization for those individuals designated and cited in this proposal.

Name	Title/Position	Total Proposed Effort
1.		
2.		

Attachment 5: Quad Chart Format Template

A quad chart must contain the following information and be positioned in a landscape view. Any quad chart submitted that exceeds the one-page limit will not be read or evaluated. Please note that the Title of the Project should be different than that of the Area of Interest.

TITLE OF PROJECT, BAA#, RESEARCH AREA OF INTEREST,
TECHNICAL/ADMINISTRATIVE POINT OF CONTACT (NAME, EMAIL, PHONE),
COMPANY NAME & ADDRESS

Objective: Clear, concise (2-3 sentences) description of the objectives and methodologies of the effort. Description of effort: A bullet list (2-3) of the primary scientific challenges being addressed	Picture or Graphic that Illustrates the research or concept (e.g. data figures, molecule illustrations or processes)
Benefits of Proposed Technology: Challenges: Maturity of Technology:	Bullet list of the major goals/milestones by Project Year Proposed Funding Base year cost plus each option year (no more than 7 years total)

Attachment 6: Government Notice for Handling & Submitting Proposals

NOTE: This Notice is for the Technical Evaluation Review Panel who will be reviewing the proposals submitted in response to this BAA. THE OFFEROR SHALL PLACE A COPY OF THIS NOTICE BEHIND THE TITLE PAGE OF EACH COPY OF THE TECHNICAL PROPOSAL.

This proposal shall be used and disclosed for evaluation purposes only, and a copy of this Government notice shall be applied to any reproduction or abstract thereof. Any authorized restrictive notices which the submitter places on this proposal shall be strictly complied with. Disclosure of this proposal outside the Government for evaluation purposes shall be made only to the extent authorized by, and in accordance with, the procedures in HHSAR 352.215-1 (Instructions to offerors—competitive acquisition).

(a) If authorized in agency implementing regulations, agencies may release proposals outside the Government for evaluation, consistent with the following:

(1) Decisions to release proposals outside the Government for evaluation purposes shall be made by the agency head or designee;

(2) Written agreement must be obtained from the evaluator that the information (data) contained in the proposal will be used only for evaluation purposes and will not be further disclosed;

(3) Any authorized restrictive legends placed on the proposal by the prospective Contractor or subcontractor or by the Government shall be applied to any reproduction or abstracted information made by the evaluator;

(4) Upon completing the evaluation, all copies of the proposal, as well as any abstracts thereof, shall be returned to the Government office which initially furnished them for evaluation; and

(5) All determinations to release the proposal outside the Government take into consideration requirements for avoiding organizational conflicts of interest and the competitive relationship, if any, between the prospective Contractor or subcontractor and the prospective outside evaluator.

(b) The submitter of any proposal shall be provided notice adequate to afford an opportunity to take appropriate action before release of any information (data) contained therein pursuant to a request under the Freedom of Information Act (5 U.S.C. 552); and, time permitting, the submitter should be consulted to obtain assistance in determining the eligibility of the information (data) in question as an exemption under the Act. (See also Subpart 24.2, Freedom of Information Act.)

Attachment 7: Breakdown of Proposed Estimated Cost (Plus Fee) and Labor Hours (For Cost Proposal)

Refer to the ASPR Business Toolkit[46] for additional supplemental guidance and templates.

INSTRUCTIONS FOR USE OF THE FORMAT

1. This format has been prepared as a guideline. It may require amending to meet the specific requirements of this BAA. If the proposal is structured using options, identify each period independently. Each period should then be broken out into sub-elements.

2. This format shall be used to submit the breakdown of all proposed estimated cost elements. List each cost element and sub-element for direct costs, indirect costs and fee, if applicable. In addition, provide detailed calculations for all items. For example:

    a. For all personnel, list the skill / labor category, rate per hour and number of hours proposed. If a pool of personnel is proposed, list the composition of the pool and how the cost proposed was calculated. List the factor used for prorating base period and the escalation rate applied between periods.
    Offeror's proposal should be stated in the same terms as will be used to account for and record the effort under a contract. If percentages of effort are used, the basis to which such percentages are applied must also be submitted by the Offeror. The attached format should be revised to accommodate direct labor proposed as a percentage of effort.

    b. For all materials, supplies, and other direct costs, list all unit prices, etc., to detail how the calculations were made.

    c. For all indirect costs, list the rates applied and the base the rate is applied to.

    d. For all travel, list the specifics for each trip.

    e. For any subcontract proposed, submit a separate breakdown format.

    f. Justification for the need of some cost elements may be listed as an attachment, i.e., special equipment, above average consultant fees, etc.

3. If the Government has provided "uniform pricing assumptions" for this BAA, the Offeror must comply with and identify each item.

4. It is requested that you use the spreadsheet that is provided below to prepare your cost proposal. For security purposes, please include a hard copy of the completed spreadsheet and submit the electronic file on a diskette with your proposal.

[46] http://www.phe.gov/about/amcg/contracts/Pages/toolkit.aspx

BREAKDOWN OF PROPOSED ESTIMATED COST (PLUS FEE) AND LABOR HOURS

Table 7: Breakdown of Proposed Estimated Cost (Plus Fee) and Labor Hours

COST ELEMENT	Period 1	Period 2	Period 3	Period 4	Period 5	
Labor Category	(Rate / Hours)	(Rate / Hours)	(Rate / Hours)	(Rate / Hours)	(Rate / Hours)	Total
DIRECT LABOR COST:	$	$	$	$	$	$
MATERIAL COST:	$	$	$	$	$	$
TRAVEL COST:	$	$	$	$	$	$
OTHER (Specify)	$	$	$	$	$	$
OTHER (Specify)	$	$	$	$	$	$
TOTAL DIRECT COST:	$	$	$	$	$	$
FRINGE BENEFIT COST: (if applicable) % of Direct Labor Cost	$	$	$	$	$	$
INDIRECT COST: % of Total Direct Cost	$	$	$	$	$	$
TOTAL COST:	$	$	$	$	$	$
FIXED FEE: (if applicable) % of Total Est. Cost	$	$	$	$	$	$
GRAND TOTAL ESTIMATED CPFF)	$	$	$	$	$	$

Attachment 8: Total Life Cycle Costs (TLCC) Definition

BARDA provides the following Total Life Cycle Costs (TLCC) definition for Offerors to consider when proposing strategies that will reduce the long term TLCC of your proposed countermeasure. BARDA is responsible for supporting advanced development of medical countermeasures (MCM) to address CBRN threats for the civilian population. To ensure long term sustainability and a robust United States preparedness and response capability, BARDA must invest in products and technologies that minimize TLCC across the PHEMCE (TRL-1 through TRL-9) and ensure long term access to the medical countermeasure. We are focused not only on the USG's TLCC but also of the TLCC of our partners, the Sponsors of the product.

BARDA seeks to identify products with 1) a sustainable commercial value in addition to biodefense applicability, which will ensure long term access to the medical countermeasure via a commercial market. 2) Products that have been optimized or will be optimized to reduce the TLCC for the proposed countermeasure throughout the products life cycle.

The following TLCC definition and below explanation of "key terms" are general guidelines for you to consider when working with BARDA.

Total Life Cycle Costs (TLCC) Definition

"The total cost to the United States Government and Sponsor of a product over its full life necessary to achieve and maintain readiness for the desired end state of the product. It may include the costs of discovery, development, acquisition, infrastructure, operations, support, and disposal."

Key Terms relevant to MCM:

- **Product**: Any MCM, technology or service being developed and/or established as a capability to support a requirement or public health emergency response capability

- **End state**: Fulfillment of a product's current requirement, concepts of operations (CONOPS) and/or Leadership's strategic goals

- **Discovery**: This includes all USG and Sponsor's costs associated with identifying candidate products and determining proof-of-concept of a product under Technology Readiness Level (TRL)1 through TRL3

- **Development**: This includes all USG and Sponsor's costs associated with Research and Development of a product from TRL4 through TRL9 [including post-licensure/approval activities]

- **Acquisition**: This includes the costs of acquiring and maintaining [e.g. re-procuring] the capability necessary to maintain readiness levels until Approval/Licensure and/or 10 years post Approval/Licensure

- **Infrastructure**: This includes the costs necessary to establish and support infrastructure [e.g. development, manufacturing, permitting, distribution and

monitoring] as required for the product

- **Operations and Support**: This includes all costs from the point the product is established as a capability [e.g. stockpile, commercial market, vendor managed inventory, ancillary supplies, etc.] through deployment of product [e.g. leaves USG possession] necessary to maintain readiness levels until Approval/Licensure and/or 10 years post Approval/Licensure. This includes operating and supporting [e.g. storage, shipment, liability relief, training, exercising, etc.] the established product until the product is removed from operational consideration

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Attachment 9: Additional Requirements Information

POINT-OF-CARE OR HIGH-THROUGHPUT BIODOSIMETRY FOR DETERMINING ABSORBED IONIZING RADIATION DOSE AFTER RADIOLOGIC AND NUCLEAR INCIDENTS

The Threat

For planning purposes, detonations of a large, improvised nuclear device (IND) in a large metropolitan locale have been modeled and used to calculate effects on the surrounding population. Such population threat assessments estimate the number of people who may require treatment for the different classes of injuries and organ-specific sub-syndromes after an incident occurs. Assessment of an individual's absorbed dose of ionizing radiation will improve triage operations, reduce the chaos and disruption of the incident, and improve the utilization of limited medical resources. Although such assessment will also be required following a radiological dispersal device (RDD) or other exposures to ionizing radiation/radioactive material, the IND scenario is likely to be the largest- and worst-case scenario driving medical countermeasure development.

CONOPs of an IND Incident

Response activities in an environment with a severely compromised infrastructure and damage to local healthcare systems for the first few days (e.g., 24 – 36 hours), when many Federal resources will likely still be en route to the incident, will place severe limitations on the provision of medical countermeasures to treat a significant number of victims. In the initial hours, only local resources and capabilities will be available. Federal personnel might not be able to arrive until 24 hours following the incident and medical treatments and diagnostic tools that must be brought in from outside the immediate area may not be fully available for 36 hours. Material assets may be available sooner from local supplies and/or Federal supplies, but it is likely that the infrastructure degradation and the presence of radiation will prevent many victims from receiving any medical attention at all for 12 or more hours. Local, state, and tribal governments will respond according to their emergency management plans. The management of conventional injuries (burn, blast and trauma) will be proceeding and may include physical decontamination that does not interfere with providing prompt medical care. Some patients with multiple injuries will be resuscitated and stabilized. Medical triage will be conducted in accordance with mass-casualty radiation triage principles, with triage continuously accomplished along every evacuation chain. Initial medical care, with the possible exception of critical stabilization to allow evacuation, will mainly be occurring at the periphery of the affected area, outside the "hot" zone in areas of low radiation exposure levels, to allow for prolonged medical intervention. Those who are not in the immediate blast area (and therefore do not sustain traumatic injuries) but who may have been exposed to fallout radiation will likely self- evacuate to surrounding areas and may seek medical care or evaluation. Given the destruction of local infrastructure, and the need for specialized burn, trauma, and acute radiation syndrome (ARS) treatment, patients requiring definitive (and potentially longer-term) care may be transferred to sites across the nation as transportation systems become available in the days to a week after the incident. More information on the response parameters (or Concept of Operations; CONOPs) for such an incident are described in the Homeland Security

Council's Planning Guidance for Response to a Nuclear Detonation[47].

At-Risk Population Needs and Considerations

As part of the charge to address the medical countermeasure requirements of the American civilian population, the unique needs of at-risk populations must be specifically considered. At- risk populations are those who have, in addition to their incident-related medical needs, other needs that may interfere with their ability to access or receive medical care[48]. The Pandemic and All-Hazards Preparedness Act of 2006 recognizes that children, senior citizens and pregnant women are such at-risk populations. Children, for example, may need immediate medical treatment when absorbed radiation doses exceed 1.5 Gy, compared to the 2 Gy threshold normally assumed, in the absence of confounding trauma, for adults. Therefore children's needs will have to be considered separately in designing biodosimetry devices and/or sorting/triage regimens. Additionally, in an IND scenario, those with limited mobility or those who are transportation disadvantaged, as well as those whose pre-existing conditions place them at increased risk of adverse health effects from radiation or have the potential to interfere with the specificity of biomarkers, should be considered particularly at-risk. Biodosimetry tools and/or sorting/triage regimens must have the flexibility to address the particular needs of these populations.

The Medical Countermeasure Requirement

For patients who are ambulatory and/or are not experiencing life-threatening trauma or illness, a comprehensive program of monitoring, physical decontamination as needed, and biodosimetry[49] will be necessary to assess the absorbed radiation dose and the potential need for immediate or forthcoming medical treatment of absorbed radiation dose and injuries. Once stabilized, those with life-threatening trauma will also need to be so assessed. Given the great numbers of individuals to be processed and the time-sensitive nature of the therapeutic window for most currently available or proposed medical countermeasures, radiation dose assessment will require a multi-phased, multi-parametric approach.

Two types of biodosimetry that will be required in this scenario are point-of-care (POC) and high-throughput (HT) biodosimetry tools that assess absorbed ionizing radiation dose utilizing biomarkers to inform initial sorting and quantitatively inform (a) triage and (b) medical treatment and patient management decisions, respectively. Field-deployable Point-of-Care (POC) devices would be utilized "in the field"[50] for initial sorting decisions and potentially to direct initial treatment dosing where available, and High-Throughput (HT) systems may be located in hospitals, other definitive care sites, or centralized laboratory facilities. Developers of these products are asked to consider how their

[47] This can be accessed at http://www3.cancer.gov/rrp/planningguidanceforresponse.pdf

[48] From the ASPR Office for At-Risk Individuals, Behavioral Health, and Human Services Coordination (ABC).

[49] For the purposes of this paper "biodosimetry" will be defined (per the Radiation Event Medical Management system) as the laboratory or clinical methods used to measure or estimate the dose of ionizing radiation energy absorbed by an individual.

[50] As described in the National Homeland Security Council's Planning Guidance for Response to a Nuclear Detonation (available at http://www.hps.org/hsc/documents/Planning_Guidance_for_Response_to_a_Nuclear_Detonation-2nd_Edition_FINAL.pdf).

particular technologies could be integrated and useful in these areas in the currently anticipated response framework for an IND incident, summarized above and found in more detail in the Homeland Security Council's Planning Guidance for Response to a Nuclear Detonation.

Preferred attributes for both the POC and HT technologies are provided below. In both cases it is desirable that the biodosimetry device use a well-qualified biomarker for absorbed radiation and that the device output can be readily interpretable and retainable, i.e., retain its information, in the subsequent weeks to months following an incident. The system will be reviewed within the regulatory processes of the Food and Drug Administration's (FDA) Centers for Devices and Radiologic Health (CDRH) and any required animal studies could have added regulatory overview under either the FDA's Center for Drug Evaluation and Research (CDER) or the Centers for Biologics Evaluation and Research (CBER).

Biodosimetry for Point-of-Care (POC) Initial Sorting

The POC diagnostic technology should (a) allow for the accurate and reproducible qualitative or quantitative determination that an absorbed radiation dose is at or above approximately 2 Gy; (b) be of low cost; and (c) as these may be field-deployed, must demonstrate feasibility for use in resource-limited settings and in triage facilities without the use of external laboratory equipment such as centrifuges, vortexes, incubators, or pipettes. These tools should allow for human sample collection (with minimal volumes, easy access, and minimal to no intervention), processing and result read-out in the same area, without the need to send samples to a central collection point for processing or testing. They should require limited sample manipulation for ease of use by minimally trained personnel (CLIA-waived devices preferred) and safe-containment of bio-hazardous material. Tools that are in routine clinical use for other indications and that could have additional tests integrated into their platform for this use are preferred. They should be able to process large numbers of samples, and they should return a result rapidly (i.e., within minutes to hours). Non-invasive or minimally invasive sample collection is preferred. The output should be in a visual format, without ambiguity, and should include a full-process negative and internal positive control. Read- outs should be readily usable as inputs into medical management protocols such as those provided by the REMM system[51]. The system must have as an integrated component a way of associating a sample taken perhaps hours earlier to the individual who provided that sample (e.g., through barcoding or other tracking mechanisms).

Biodosimetry for High-Throughput Triage and Definitive Care Management

The High-Throughput biodosimetry should provide a quantitative, accurate and reproducible determination of absorbed radiation dose (within the range of 0.5 – 10 Gy) useful for informing triage and definitive care decisions and should be insensitive to therapeutic interventions that may have begun for the patient prior to testing. Read-outs should be readily usable as inputs into medical management protocols such as those provided by the REMM system (www.remm.nlm.gov). These assays could be utilized at the sites of definitive care (hospitals etc) where patients are seeking medical care either following self-evacuation or transfer as transportation systems become available, or could be located in centralized laboratory facilities receiving samples from these

[51] Radiation Emergency Medical Management - http://www.remm.nlm.gov/

definitive care sites in the weeks following an incident. Systems in which samples are obtained remotely and brought in for analysis are acceptable and, while minimally invasive sample collection is still preferred, more invasive techniques can be considered if offset by other system advantages. Assay systems should be easily operated by trained clinical laboratory personnel. Systems that are in routine clinical use for other indications and that could have additional tests for these indications integrated into their platform are preferred. The system must have as an integrated component a way of associating a sample taken perhaps at a different location to the individual who provided that sample (e.g. through barcoding or other appropriate tracking mechanisms). Tracking systems that integrate with other patient medical record systems are preferred.

ACUTE RADIATION SYNDROME SCENARIO-BASED REQUIREMENTS

Due to the complexity of radiation-induced injury, the civilian requirement for medical countermeasures is a suite of countermeasures to increase survival from ARS and DEARE. This suite of countermeasures will need to address the hematopoietic syndromes, gastrointestinal syndrome, lung injury and those requiring treatment for skin/radiation burns. The quantities of each medical countermeasure to be acquired, and the ideal and minimal characteristics for each, are currently under evaluation by HHS. More information will be provided as it is available.

The details of the medical countermeasures would greatly impact how the agent(s) would be procured, stockpiled, resource-shared, vendor-managed, or otherwise made available.

Because radiation injury is a cascade of incidents that is initiated at the time of exposure, improved outcomes will require as prompt delivery of drugs as possible. Therefore, some pre- positioning in multiple sites across the country is anticipated, which will affect the total number of treatment courses of particular medical countermeasures that will be required ("procurement requirement"). The characteristics of the medical countermeasure, including whether it is in general clinical use to allow for resource sharing and possibly vendor-, distributor-, or user- managed inventory, and other considerations will determine both the deployment and reload numbers.

Medical response will require that the SNS or other sources have an adequate quantity of medical supplies and countermeasures including those needed for burns, trauma, combined injury, and infection, as well as radiation injury. Specific requirements for these are being developed.