Department of Health & Human Services (HHS)
Assistant Secretary for Preparedness & Response (ASPR)
Biomedical Advanced Research and Development Authority (BARDA)

BAA-13-100-SOL-00019

Broad Agency Announcement for the Advanced Development of Medical Countermeasures for Pandemic Influenza

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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, Room G640, 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, 330 Independence Avenue SW, Room G640, Washington, DC 20201

Research Opportunity Title: Broad Agency Announcement for the Advanced Development of Medical Countermeasures for Pandemic Influenza

Announcement Type and Date:
Broad Agency Announcement renewal, 2013, BAA-13-100-SOL-00019.

Previous Announcements as BARDA-11-100-SOL-00021, issued June 20, 2011 and expired April 10, 2012; and BARDA-12-100-SOL-00018, issued June 8, 2012 and expired June 7, 2013.

This BAA is available on the following web sites:
https://www.fbo.gov
https://www.medicalcountermeasures.gov
http://www.phe.gov

Interested parties are encouraged to periodically check these web sites for updates and amendments to this BAA as they occur.

Eligible Applicants: This BAA is open to **ALL** responsible sources. Offerors may include private sector organizations, Federal, State or Local Government laboratories, Federally Funded Research and Development Centers (FFRDCs), academic institutions, and other non-for-profit organizations. Offerors have the option of creating teams with other organizations.

Federally Funded Research and Development Centers (FFRDCs) are eligible to respond to this BAA, individually or as a team member of an eligible principal Offeror, so long as they are permitted to do so under the sponsoring agreement between the Government and the specific FFRDC.

To be eligible for award, a prospective recipient must meet certain minimum standards pertaining to financial resources, as well as a demonstrated ability to accomplish the proposed performance schedule. The Offeror must also demonstrate the following capabilities: a prior record of performance, integrity, organization, experience, operational controls, technical controls, technical skills, facilities, and equipment.

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

Research Opportunity Description: The Biomedical Advanced Research and Development Authority solicits the advanced research and development of medical countermeasures to protect the civilian population of the United States against pandemic influenza. BARDA anticipates that research and development activities awarded under this BAA will serve to advance candidate medical countermeasures towards licensure or approval by the Food and Drug Administration (FDA).

Background

This Broad Agency Announcement (BAA) sets forth advanced development areas of interest for the Influenza Division of the Office of the Biomedical Advanced Research and Development Authority (BARDA), a component of the Office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. This BAA is issued under paragraph 6.102(d)(2) of the Federal Acquisition Regulation (FAR), and proposals selected for award are considered to be the result of full and open competition and in full compliance with the The Competition in Contracting Act of 1984, 10 U.S.C.§ 2304.

BARDA is the lead Federal agency for the advanced development of medical countermeasures (MCM) to protect the United States against public health emergency threats, including chemical, biological, radiological and nuclear agents, emerging infectious diseases, and pandemic influenza. The Pandemic and All Hazard Preparedness Reauthorization Act directs BARDA to promote (i) innovations in technologies that may assist MCM advanced research and development, (ii) research and development of tools, devices, and technologies, and (iii) research to promote strategic initiatives, such as rapid diagnostics, broad spectrum antimicrobials, and vaccine manufacturing technologies. The priorities of the BARDA Influenza Division are closely aligned with the *National Strategy for Pandemic Influenza* (November 2005), the *National Pandemic Influenza Implementation Plan* (May 2005), *The Public Health Emergency Medical Countermeasures Enterprise Review* (August 2010), the President's Council of Advisors on Science and Technology report on influenza vaccine manufacturing (August 2010), and the *BARDA Strategic Plan 2011-2016* (October 2011).

The 2009 H1N1 influenza pandemic exemplified the unpredictability and rapidity with which a novel influenza strain can impact the world's population. With a historic effort from both Government and industry partners, vaccines were developed and available to the public six months after the initial outbreak. Despite high infection rates, the 2009 H1N1 virus was only mildly pathogenic, with relatively low rates of accompanying morbidity and mortality in the general population. However, it is possible that future pandemics will feature morbidity and mortality rates comparable with more severe pandemics such as 1918 and 1957. The ever-present and ever-evolving threat of novel influenza subtypes such as H5N1 and H7N9 highlights the need to continue optimizing available medical countermeasures and developing entirely new modalities for prevention and treatment of influenza disease.

Vaccines, therapeutics, diagnostics, and devices are essential for protecting all segments of the civilian population. This BAA will support advanced development activities to mature candidate products and to better address considerations of the

challenging lifecycle requirements of these products before and during a pandemic (e.g., shelf life, storage, distribution, and dispensing). Additional focus will be placed on medical countermeasures and devices suitable for use in at-risk populations such as children, pregnant women, the elderly, and persons with compromised immune systems. BARDA will endeavor to prioritize projects that provide benefits to all populations while also allowing for focused development projects or studies for at-risk populations where necessary.

Guidance for Potential Offerors

Areas of Interest

This BAA solicits proposals that focus on one or more of the following areas of interest as listed here and further described in Part I of this announcement.

Development Areas of Interest:

1. Personal Protective Equipment (Masks and Respirators) for Influenza Infection & All-Hazards
2. Full-Featured Continuous Ventilators for Influenza Infection and All-Hazards
3. Clinical Influenza Test Systems and Diagnostic Tools
4. Influenza Therapeutics
5. Influenza Vaccines
6. Influenza Vaccine Manufacturing Improvement

Technical objectives are described in Part II, and Offerors may propose activities in one or more areas (e.g., Non-Clinical Product Development, Manufacturing Process Development, Formulation, 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 Development 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. Please 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 vaccines and therapeutics, one with devices, and two TRL documents are provided to evaluate diagnostic products and to provide Offerors greater insight into the complexities of the diagnostics development process. Either diagnostics TRL criteria document may be used to assess the maturity of a diagnostic product.

Application Process

The BAA review process will be conducted in two stages:

In **Stage 1**, Offerors shall submit a Quad Chart and White Paper summarizing the proposed project. All Quad Charts and White Papers must be prepared in accordance with the instructions contained in Part IV. Brochures or other descriptions of general organizational or individual capabilities will not be accepted. Electronic acknowledgement of receipt of White Papers will be made within one week.

For Stage 1, there are four quarterly deadlines: October 30, 2013; January 30, 2014; April 30, 2014; and July 30, 2014, at 4:30PM EST on each date. Offerors who submit White Papers after a given deadline may not have their materials reviewed until after the next deadline. **Quad Charts and White Papers will not be accepted after 4:30PM Eastern Standard Time on July 30, 2014.**

Following BARDA review, decision letters will be sent to Offerors within 90 calendar days after the deadline with a decision to invite or not invite for a Full Proposal.

In **Stage 2**, Offerors receiving a favorable Stage 1 evaluation will be invited to submit a Full Proposal to BARDA by a date specified by the Contracting Officer in the proposal invitation letter. Instructions for preparing the Full Proposal are found in Part IV of this announcement. A request to submit a Full Proposal is not a guarantee of an award.

The success of a product development program requires a relentless focus on the desired characteristics of the resulting medical countermeasure product or device. As a component of a Full Proposal submission, Offerors are requested to provide a Target Product Profile if applicable. A template for a Drug Target Product Profile is included in Attachment 7 as a guide for Offerors to describe the objectives of their advanced research and development activities, and to be updated dynamically as supporting data about their product or project is obtained. All Offerors are encouraged to submit a Target Product Profile for the proposed medical countermeasure or device, 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 desired outcome of the proposed development activities should be provided.

There are no specified funding limitations identified for individual proposals submitted under this BAA. The budget shall be commensurate with the nature and complexity of the proposed activities; however, contract awards and level of funding may be impacted by the availability of Congressional annual and/or supplemental appropriations. The costs of preparing responses to this BAA are not considered an allowable direct charge on any resultant award.

Communicating with BARDA

In an effort to more effectively meet its mission, BARDA has developed a Technology Watch seminar series where product developers can meet with US Government staff and present their candidate technologies. During these talks, Government officials can provide informal feedback on product development activities. Before applying for this solicitation, product developers are highly encouraged to provide a Technology Watch seminar at BARDA. Offerors who have a Quad Chart and White Paper or Full Proposal currently under evaluation may not present a Technology Watch seminar until their submission has been adjudicated. Requests to schedule a meeting can be submitted at:

https://www.medicalcountermeasures.gov/Request-Meeting.aspx

BARDA realizes that the preparation of a research 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 to make preliminary inquiries as to the appropriateness of their technology to this solicitation before preparing a Quad Chart and White Paper. **Offerors contemplating a Quad Chart and White Paper submission are strongly encouraged to contact BARDA technical staff at FLU-**

BAA@HHS.GOV. In order to ensure a timely response, the subject line of each e-mail must include either the number of the Development Area of Interest in question, or "ADMIN" to indicate administrative and process questions. Please include all necessary contact information with any inquiry.

Once a White Paper or Full Proposal has been submitted, all communications should be conducted with the appropriate Contracting Officer in The Office of Acquisition Management, Contracts & Grants (AMCG). Offerors are advised that only a Contracting Officer may obligate the Government to any agreement involving expenditure of Government funds.

Contractual Guidance

In accordance with Federal statutes, regulations, and HHS policies, no person on grounds of race, national origin, color, religion, sexual orientation, gender identity, disability (physical or mental), age, status as a parent, or genetic information 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 HHS.

BARDA reserves the right to fund all, some, or none of the proposals submitted. While awards are anticipated to occur according to the stated schedule, Offerors that are not responsive to BARDA requests for information in a timely manner, or fail to meet Government deadlines established and communicated with each request, may be removed from award consideration. BARDA reserves the right to award the instrument best suited to the nature of the research proposed and may award any appropriate contract type permitted under the Federal Acquisition Regulation.

Anticipated funding for this solicitation (not per contract or per award) may range from $2M to $300M subject to Congressional appropriations. **This funding amount does not reflect potential funding amounts for single contract awards.** Multiple awards of various values are anticipated and are dependent upon the proposals' scientific and technical merits applicability to BARDA's areas of interest and prioritized program objectives. This funding profile is an estimate only and does not represent a contractual obligation for funding. All funding is subject to change due to Government discretion and availability.

The purpose of this BAA is to support advanced development of medical countermeasures for pandemic influenza. This solicitation does not include any provisions for acquisition of products. Support for advanced development of any particular product through this solicitation should not be viewed as a precursor to a future acquisition. Offerors should therefore assume the responsibility for developing a commercial market for any product developed using BARDA funding.

All administrative and technical inquires regarding this BAA shall be addressed to FLU-BAA@hhs.gov. **In order to ensure a timely response, the subject line of each e-mail must include either the Development Area of Interest in question, or "ADMIN" to indicate administrative and process questions.** Please include all necessary contact information with any inquiry.

This BAA is a continuously open announcement valid throughout the period from the date of issuance through July 30, 2014, unless announced otherwise. Amendments to

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

Part I: Development Areas of Interest

This section presents an overview of the influenza-related 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 staff at FLU-BAA@HHS.GOV. In order to ensure a timely response, the subject line of each e-mail must include either the Development Area of Interest in question, or "ADMIN" to indicate administrative or process questions.

Note to Potential Offerors: Due to the urgency of ongoing preparedness activities for avian influenza A(H7N9) virus, available funding for awards under this solicitation may be limited. In addition, submissions that directly address H7N9 preparedness may be evaluated more favorably than those directed towards other influenza subtypes.

Area of Interest #1: Personal Protective Equipment (Mask & Respirators) for Influenza Infection and All-Hazards

Offerors for Area of Interest #1 should describe the maturity level of their proposed technology. The Technology Readiness Level ranking criteria can be found in Attachment 1B of this solicitation. Proposed activities should offer clinical and public health benefits.

1.1 Development and characterization of improved respiratory protective devices (RPD). Support for advanced development of improved RPD such as masks or respirators to prevent influenza infections or harmful effects of biological hazards. RPD demonstrate improved features over currently available devices for functionality, usability, comfort, decontamination and re-use, cost efficiency, and durability to support a broad population (e.g., pediatric through adult), with a clear path to NIOSH certification and FDA clearance as applicable.

Area of Interest #2: Full-Featured Continuous Ventilators for Influenza Infection and All-Hazards

Offerors for Area of Interest #2 should propose activities for products which can currently be described as having a maturity level equal to or greater than Technology Readiness Level (TRL) 6. A product can be described as achieving a TRL if it has completed all activities identified in that TRL. The Technology Readiness Level ranking criteria can be

found in Attachment 13B of this solicitation. Proposed activities should offer beneficial clinical and public health impact.

2.1 Development of improved full-featured continuous ventilators. Advanced development of new or improved ventilators to provide life support in clinical and non-clinical environments for severe respiratory conditions resulting from influenza infections or all-hazards events. Ideal ventilators should support neonate to adult populations, be capable of operation by unskilled or minimally trained care providers, include considerations for ease of stockpiling/maintenance, accommodate/provide accessories typically used in ventilatory standard of care, have a low cost per unit (<$3,000 per fully-kitted unit), and accommodate domestic surge production capacity.

Area of Interest #3: Clinical Influenza Test Systems and Diagnostic Tools

Offerors for Area of Interest #3 should propose activities for products which can currently be described as having a maturity level equal to or greater than the Technology Readiness Level (TRL) indicated below. A product can be described as achieving a TRL if it has completed all activities identified in that TRL. For diagnostics, two TRL criteria are provided in Attachments 1A and 1B of this solicitation; offerors may use either one to rate the maturity of their technology. Design, manufacturing, and assembly of reagents and system components proposed must be consistent with U.S. Quality Systems Regulations (21 CFR Part 820) and use in CLIA-regulated laboratories. Proposed activities should offer beneficial clinical and public health impact.

3.1 Development of improved respiratory specimen collection materials and methods. Approaches should enable direct testing (using viral antigen or nucleic acids) and evaluation in on-site laboratories, with available transport systems to maintain viability and nucleic acid integrity for reference and confirmatory testing. Materials and methods can enable reliable and consistent self-collection or collection by non-expert personnel.

3.2 Development of advanced sequence detection methods for identifying novel influenza strains. Advanced development and implementation of methods applying targeted or whole genome sequencing for known influenza reassortant genes to enable more rapid identification of human-animal reassortant influenza viruses, with the goal of diagnosis of unusual influenza infections. Critical technology component should be at a maturity level equal to or greater than TRL 6.

3.3 Development of expanded respiratory pathogen tests on existing test platforms. Transfer and validation to existing platforms of established molecular or other target signatures for influenza and other respiratory pathogens. Critical technology component should be at a maturity level equal to or greater than TRL 8.

3.4 Rapid identification of antiviral resistant influenza strains. Advanced development of reagents for reference methods to identify antiviral resistance and standardize functional resistance testing; adaptation of these methods for use in clinical hospital laboratories, with interpretive criteria correlating to clinical outcomes in patients with antiviral resistant infections.

NOTE: Development programs at lower maturity levels should consider funding opportunities offered by The National Institute of Allergy and Infectious Diseases (NIAID) or other Federal agencies that fund earlier stage research and development projects. Information about NIAID resources can be found at:
http://www.niaid.nih.gov/topics/diagnostics/Pages/funding.aspx

Technical inquiries about funding through NIAID programs can be directed to:
DMIDResources@niaid.nih.gov

Area of Interest #4: Influenza Therapeutics

Offerors for Area of Interest #4 should propose activities for products which alone or in combination can currently be described as having a maturity level equal to or greater than Technology Readiness Level (TRL) 6. A product can be described as achieving a TRL if it has completed all activities identified in that TRL. The Technology Readiness Level ranking criteria can be found in Attachment 1C of this BAA.

4.1 Antiviral Therapeutics for Treatment of Influenza A & B Infection.

Advanced development of antiviral therapeutics at TRL6 or greater with a novel mechanism of action relative to currently approved anti-influenza therapeutics. Small molecule compounds, monoclonal antibodies, therapeutic proteins, peptides or oligonucleotides proven to reduce influenza virus replication in cell culture and animal models are examples of therapeutics that would be considered. Therapeutics with a mechanism of action that precludes the rapid emergence of drug resistance and with proven broad influenza strain susceptibility are preferred. Combination therapeutics that include novel investigational compounds and licensed therapeutics would also be applicable.

NOTE: Development programs at a maturity level less than TRL6 should consider funding opportunities offered by The National Institute of Allergy and Infectious Diseases (NIAID) or other Federal agencies that fund earlier stage research and development projects.

Information about NIAID resources can be found at:
http://www.niaid.nih.gov/LabsAndResources/resources/dmid/Pages/therapeutics.aspx

Technical inquiries about funding through NIAID programs can be directed to:
DMIDResources@niaid.nih.gov

Area of Interest #5: Influenza Vaccines

Offerors for Area of Interest #5 should propose activities for products that can currently be described as having a maturity level equal to or greater than Technology Readiness Level (TRL) 6 (e.g. as evidenced by release of a finalized report for a Phase 1 clinical study for the same indication as proposed activities). A product can be described as achieving a TRL if it has completed all activities identified in that TRL. The Technology Readiness Level ranking criteria can be found in Attachment 1C of this BAA.

Under this Area of Interest, BARDA is seeking technologies that will improve preparedness against influenza subtypes with pandemic potential. Successful offerors will provide evidence of vaccine approaches that show improvement in key vaccine attributes as compared to currently available products.

5.1 Advanced development of novel influenza vaccine candidates which have achieved TRL 6 or greater. Support for advanced development of novel influenza vaccine candidates with the potential to stimulate a broader and more effective immune response than currently available products. Data should be provided that demonstrates statistically-relevant improvements in immunogenicity/efficacy as compared to existing vaccines. Proposed activities should enable improvements to key vaccine attributes, including dose schedule, time to onset of protection, induction of improved immunogenicity, broader cross-protection across influenza A virus subtypes, and duration of protection. Use of approved or novel adjuvants to achieve enhanced or broadened immunogenicity may also be a component of the advanced development program.

Development programs at a maturity level less than TRL 6 should consider funding opportunities offered by The National Institute of Allergy and Infectious Diseases (NIAID) or other Federal agencies that fund earlier stage research and development projects.

Information about NIAID resources can be found at:
http://www.niaid.nih.gov/LabsAndResources/resources/dmid/vaccine/Pages/default.aspx

Technical inquiries about funding through NIAID programs can be directed to:
DMIDResources@niaid.nih.gov

Area of Interest #6: Influenza Vaccine Manufacturing Improvement

At this time BARDA is not accepting any submissions for Area of Interest #6.

Part II: Technical Objectives

The topics listed below exemplify some of the typical activities undertaken during a drug, biologic or device development effort in the areas of non-clinical studies, manufacturing, clinical evaluation, project management, and regulatory strategy. This information is provided to assist and guide Offerors in preparing their White Papers and Full Proposal Statements of Work (SOW).

Offerors should submit information in their White Paper and Full Proposal that addresses these topics as appropriate, and should provide as much detail as may be necessary to fully explain and justify the proposed technical approach or method. **Offerors should propose a SOW consistent with activities for the Technology Readiness Level indicated for each Development Area of Interest in Part I.** The SOW must be presented in discrete segments that are non-severable in their activity.

Proposal preparation and submission instructions are contained in Part IV.

A. Development Approach:

Personal Protective Equipment (PPE) and Full-Featured Continuous Ventilator Activities may also include but are not limited to:

a. Integration and Verification:
- Establish technical specifications based on design controls.
- Establish qualification of components and accessories.
- Produce pre-production (beta) prototype.

b. Internal and External Validation Studies:
- Design and validate performance test protocols and acceptance criteria (e.g., bench, animal and/or clinical studies) to enable standardized safety and effectiveness measures.
- Conduct field evaluations of PPEs to filter influenza viruses and other respiratory hazards.
- Conduct field evaluations of ventilators to provide respiratory support in comparison to predicate devices on the market.

c. Manufacturing:
- Produce pilot or finished lots of test units in sufficient quantities for clinical and non-clinical evaluations.
- Maintain appropriate quality assurance with processes, procedures, and documentation consistent with design controls (as applicable), Quality Systems, and relevant standards (e.g., deviation and risk management strategies).
- Identify critical manufacturing process parameters for domestic scale-up production.

d. Other Product Development Activities:
- Collaborate with relevant technical guidance and standards organizations to develop consensus test methods and parameters.
- Provide equipments and/or necessary materials along with technical support to programs evaluating the safety and effectiveness of these devices in relevant environments.
- Evaluate therapeutic value of ventilator features for assisting clinical decisions.

- Design and coordinate conduct of clinical evaluations including device performance and usability by non-skilled or minimally trained care providers in collaboration with institutional or public health programs.
- Incorporate universal breathing circuits and interoperable ventilator accessories for increased compatibility with broad range of accessory components.

Influenza Test System and Diagnostic Tool Activities may also include but are not limited to:

a. Integration and Verification:
- Establish QA criteria based on implemented design controls.
- Produce pre-production (beta) instrument platform
- Initiate accelerated and real-time stability studies
- Establish technology transfer agreements and implement qualification of sourced reagents, components, and materials.

b. Internal and External Validation Studies:
- Develop assessments of specimen processing methods and specimen target stability using modified or new collection and transport materials.
- Collaborate with clinical entities to assess feasibility for use of specific specimen collection methods.
- Optimize new or modified assays on existing platforms.
- Design and validate protocols for analytical and clinical studies to enable standardized performance measures.
- Perform field evaluations with rapid *in vitro* diagnostic test systems to detect and identify influenza viruses and optionally distinguish other respiratory pathogens.

c. Manufacturing:
- Produce pilot or finished lots of test units (e.g., cartridges, assay plates) in sufficient amounts for clinical and non-clinical evaluations
- Maintain appropriate quality assurance with processes, procedures, and documentation consistent with design controls (as applicable), Quality Systems, and relevant standards (e.g., deviation and risk management strategies).
- Identify critical manufacturing process parameters for scale-up production.

d. Other Product Development Activities:
- Use publicly available gene sequences in collaboration with CDC, NIH and others with advanced influenza genetic informatics expertise to characterize influenza viruses for device, assay, or test design.
- Collaborate with guidance and standards organizations to develop laboratory and practice guidance or standards for specific methods.
- Evaluate specimen types, test methods, and testing algorithms for assessing positive and negative likelihood ratios of influenza infections in specific clinical settings.
- Evaluate diagnostic value of respiratory disease test methods for informing clinical management decisions.

- Provide equipment, reagents and necessary materials along with technical support, as requested, to programs monitoring influenza prevalence and characterizing circulating virus types, subtypes, and resistance.
- Design and coordinate clinical evaluations in collaboration with institutional or public health programs to monitor influenza virus and other respiratory pathogens causing community respiratory disease outbreaks.
- Validate clinical assessment strategies for guiding influenza testing decisions in outpatient practice, to include at-risk groups (e.g., pediatrics and obstetrics).

Therapeutics Advanced Research and Development Representative Activities may include but are not limited to:

a. Expand assessment of antiviral potential for therapeutics previously approved for other indications.
b. Evaluation of the safety, efficacy, pharmacokinetics, pharmacodynamics, bioavailability, solubility, formulation, dose, route and schedule of novel or reformulated countermeasures.
c. 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.
d. Development of validation protocols for analytical and assay methods to define product manufacturing control, performance, potency and product stability indication.

Therapeutics Process Development, Formulation, and Manufacturing Development Representative Activities may 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, and quality, and to reduce the variability and risk factors in the manufacturing of the drug substance and drug product.
c. Formulation development to evaluate combinations of excipients and their influence on product characteristics and on product stability.
d. Manufacture of GMP lots of candidate products in amounts sufficient to carry out required/proposed 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. Development of Risk Evaluation and Mitigation Strategies or similar risk mitigation strategy proposals

k. Manufacturing/Testing facility plan to support clinical trial lots through commercial scale product supply, including consideration of capacity for surge manufacturing in the event of an influenza pandemic

Therapeutics Clinical Evaluation Representative Activities may include but are not limited to:

a. Design and conduct of clinical trials (Phase 2, and/or 3) to evaluate candidate medical countermeasure and device products 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 clinical trials to evaluate safety and/or efficacy of candidate products in at-risk populations (e.g., elderly, pediatric, or immunocompromised persons).
c. Development of a clinical development plan that outlines key milestones and activities to mature the candidate product through FDA approval/licensure.
d. Design and conduct clinical trials to evaluate optimal use of influenza antivirals or immunomodulators for informing clinical and public health management decisions.

Vaccine Advanced Research and Development Representative Activities may include but are not limited to:

a. Limited evaluation in ancillary nonclinical studies as required to support proposed activities with a maturity of TRL6 or greater.
b. 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 required for these assays.
c. Development of validation protocols for analytical and assay methods to define product manufacturing control, performance, potency and product stability indication.

Vaccine Process Development, Formulation, and Manufacturing Development Representative Activities may 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, and quality, and to reduce the variability and risk factors in the manufacturing of the drug substance and drug product.
c. Formulation development to evaluate combinations of excipients and their influence on the target product profile and on product stability.
d. Manufacture of GMP lots of candidate products in amounts sufficient to carry out required/proposed clinical trials that would seek to enhance the effectiveness of existing biologics and pharmaceuticals.
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. Development of Risk Evaluation and Mitigation Strategies or similar risk mitigation strategy proposals
k. Manufacturing/Testing facility plan to support clinical trial lots through commercial scale product supply, including consideration of capacity for surge manufacturing in the event of an influenza pandemic

Vaccine Clinical Evaluation Representative Activities may include but are not limited to:

a. Design and conduct of clinical trials to evaluate candidate medical countermeasure and device products in humans in accordance with Good Clinical Practice guidelines (GCP: as defined by 21 CFR §312 and ICH Guidelines document E6). Clinical trial activities can be conducted at domestic or international sites, given appropriate justification.
b. Design and conduct of clinical trials to evaluate safety and/or efficacy of candidate products in at-risk populations (e.g., elderly, pediatric, or immunocompromised persons).
c. Evaluation and validation or correlation of clinical and/or immunological endpoints to support the development of broadly reactive ("universal") influenza vaccines, including innate and adaptive immunity, both humoral and cellular.
d. Development of a clinical development plan that outlines key milestones and activities to mature the candidate product through FDA approval/licensure.

Development programs at a maturity level less than that indicated for each Development Area of Interest should consider funding opportunities offered by The National Institute of Allergy and Infectious Diseases (NIAID) or other Federal agencies that fund earlier stage research and development projects.

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. **Integrated Product Development Plan**
   Within thirty (30) calendar days of the effective date of the BAA award, the Contractor shall submit an Integrated Product Development Plan (IPDP), which includes a summary of all key program activities, milestones, and "go/no-go" decisions. The Contractor should submit one (1) paper copy and one (1) electronic copy to the Contracting Officer and Contracting Officer's Representative (COR). **The IPDP must be approved by the Contracting Officer and the COR prior to initiation of any activities under the contract.**

2. **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 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.

3. **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.

Risk Management Plan:
The Contractor should develop a risk management plan to identify and monitor potential risks that may arise during the life of the contract, to quantify the impact of these risks on cost, schedule and performance, and to propose appropriate mitigation and remediation plans. This plan should reference relevant key milestones and activities where appropriate. The format for such a plan and timeline for submission will be determined during contract negotiations.

Additional reports may be 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:

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.

BARDA 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.

Earned Value Management Plans and Documentation:

Depending on the nature and scope of the contract awarded, BARDA may require the Contractor to implement an Earned Value Management (EVM) system to monitor contract performance and link milestone achievements with contract expenditures. The requirements below are typical components of implementing an EVM system under a BARDA contract, but specific parameters will be defined during contract negotiation.

An Integrated Master Schedule (IMS) [Gantt chart] should be developed by the Contractor and used to monitor performance of the contract. The Contractor should incorporate key product development milestones, go/no go decision points, and decision gates into the contract. The IMS for the period of performance should be developed concurrently with the IPDP, and will be reviewed and approved by BARDA following contract award.

During the course of contract performance, in response to a need to change the 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:

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.

Additional program management information and templates are available online under AMCG Business Toolkit (http://www.phe.gov/about/amcg/toolkit/Pages/default.aspx)

Part IV: Proposal Preparation and Submission

Section 1: The Application Process

The application process is in two stages as follows:

Stage 1: Prepare a cover sheet, Quad Chart, and White Paper 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. BARDA will evaluate White Papers based on the criteria provided in Part V.

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 debriefing that will be provided to unsuccessful Stage 1 Offerors.

Stage 2: Offerors must submit their Full Proposals in accordance with the instructions provided below. Full Proposals will be evaluated against criteria as described in Part V. 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.

Proposal Stage	Deadline for Submission	Government Response
Stage 1: Quad Chart and White Paper	October 30, 2013 January 30, 2014 April 30, 2014 July 30, 2014	Receipt confirmation within 1 week. Decision within 90 calendar days of submission deadline.
Stage 2: Full Proposal	Deadline will be specified in the Full Proposal invitation letter	Receipt confirmation within 1 week.
Source Selection Notification (pending availability of funds)		Decision within 180 calendar days of receipt of Full Proposal or final revised proposal.

Section 2: Stage 1 Quad Chart and White Paper Preparation

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. **This results in a submission packet not to exceed 14 pages.** If submissions exceed these limitations, only those pages that fit within the above limits will be reviewed.

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

Quad Chart Format:
All Quad Charts should include the information indicated on the sample template located in Attachment 6. All Quad Charts should be laid out in landscape format.

1. Heading: Title, Development Area of Interest, Offeror point of contact, Company's Name
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, cost.

White Paper Format:

1. The White Paper should provide a brief technical discussion of the Offeror's objective(s), 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 regarding the alignment of the proposed project with the objectives of the BAA, the development area of interest that the submission is responding to, and key strategic documents including the National Strategy for Pandemic Influenza, the HHS Pandemic Influenza Implementation Plan, and the BARDA Strategic Plan. (This portion of the white paper should be concise so that the majority of the document can address the maturity of the technology and the proposed product development plan.)
    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 clear and concise description of the intellectual property status of the relevant technology or technologies.
    f. An overview of the Offeror's capabilities and experience as they relate to executing the proposed development activities.
2. A two-page addendum to the White Paper should be provided that includes brief biographical sketches of the key personnel who will be performing or managing project activities,highlighting their relevant qualifications and experience. Any applicable references should also be cited if they are relevant to the proposed work plan.

Restrictive markings on White Papers: 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 that they do not want disclosed

should mark their submission in accordance with the instructions contained in FAR 52.215-1(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 solely for evaluation and possible award by other agencies.**

Section 3: Stage 1 Quad Chart and White Paper Submission

White Papers should be submitted by e-mail to FLU-BAA@hhs.gov

Include "BARDA INFLUENZA BAA QUAD CHART & WHITE PAPER for Development Area #__" in the e-mail subject line. White Papers do not require any special forms, but must be submitted in the following format:

- Single PDF file as an e-mail attachment
- Page Size: 8 ½ x 11" with 1" Margins
- Spacing – single
- Font – Arial, 12 point

IMPORTANT NOTE: The title given to the White Paper should be descriptive of the work proposed and not be merely a copy of the title of this solicitation.

The file size should not exceed 10 megabytes. Movie and sound file attachments, URL Links, or other additional files will not be accepted (with the exception of cited references).

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

Notification to Offerors: All Offerors will receive an e-mail acknowledging receipt of their Quad Chart and White Paper submission. Offerors will receive an e-mail within 90 calendar days of the submission deadline informing them whether or not they will be invited to submit a Full Proposal. (Offerors may receive a decision letter sooner than 90 calendar days depending on the number of White Papers submitted to BARDA or if otherwise specified in an amendment to the BAA). Offerors who submit white papers after a given submission deadline may not have their materials reviewed until after the next submission date. Debriefings for Quad Charts and White Papers not invited for full proposals will not be provided, however, technical feedback will be provided in the response letter from BARDA.

Section 4: Stage 2 Full Proposal Preparation

Following a successful Stage 1 review, 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 their invitation letter. Offerors may contact the Contracting Officer to schedule teleconferences.

The Full Proposal must be prepared as four separate volumes as follows: Volume I Technical Proposal; Volume I Technical Proposal Appendices; Volume II Cost Proposal; and Volume II Cost Proposal Appendices.

A. Volume I - Technical Proposal

The technical proposal Volume I page limit is 50 pages (excluding items 1-3 below) , with 70 pages of appended material *unless otherwise specified in the invitation*, including figures, tables and graphs, for a total length of 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 12 point font. This should include the following items:

1. Technical Proposal Cover Sheet: This should include the words "Technical Proposal" and the following:
   a. BAA number
   b. Title of proposal (descriptive of the work proposed and not a copy of the title of the solicitation)
   c. Date of submission
   d. Identity of prime Offeror and complete list of subcontractors and consultants, if applicable
   e. Technical contact (name, address, phone/fax, e-mail address)
   f. Administrative/business contact (name, address, phone/fax, e-mail address)
   g. Proposed period of performance

2. Official Transmittal Letter including:
   a. The name, title, mailing address, telephone number, and fax number of the company or organization;
   b. The name, title, mailing address, telephone number, fax number, and e-mail address of the point of contact regarding decisions made with respect to the Offeror and who can obligate the proposal contractually;
   c. The name, title, mailing address, telephone number, fax number, and e-mail address and those individual(s) authorized to negotiate with the USG; and
   d. A statement indicating you are submitting a Full Proposal for consideration under this solicitation.

3. Table of contents: an alphabetical/numerical listing of the sections within the proposal, including corresponding page numbers.

4. Executive Summary (limit to one page)

5. Statement of Work: 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 include 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 and subtasks organized by phases (base and option segments).

6. 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 pursued if the initial methods do not achieve the defined goals. Previous results and data should be included as necessary to justify the proposed development activities.

7. Gantt Chart/Work Breakdown Structure (WBS), including key project activities, milestones, and “go/no-go” decision points

8. Deliverables: A detailed description of the results and products to be delivered inclusive of the timeframe in which they will be delivered (in addition to and inclusive of those outlined in Part III).

9. 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 or summary biosketches 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.

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

11. A listing of Contractor-provided facilities, infrastructure and other resources applied to the proposed activities and tasks. Depending on the stage of development of the candidate product, this may include but is not limited to:
    a. Current facility design including quality control labs for testing & release, laboratory areas supporting formulation and assay development, manufacturing process flow, and animal studies.
    b. Major equipment and layout (e.g., preliminary piping and instrumentation drawing).
    c. Manufacturing capacity expansion plans to match the proposed scale.
    d. Overview of the management of Quality Systems at the facility.
    e. List of capabilities for clinical activities managed in-house and/or by contract research organizations; list of clinical sites engaged for product evaluations.
    f. Qualified animal facilities where GLP studies would be conducted and appropriate certifications for humane care and use of vertebrate animals.
    g. 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.
    h. Validation master plan for key equipment, analytical methods and manufacturing process.

i. commercial capabilities of the Offeror, including current products, and marketing, distribution and customer support capabilities (as applicable)
j. List of key vendors or service providers, locations, and brief description of their expertise/experience.

12. 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.

13. 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.

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.

14. The Offeror must also represent that they have adequately addressed the following requirements (as appropriate):
    a. research involving human subjects/anatomical substances
    b. research involving animals
    c. evidence of GLP compliance
    d. evidence of GMP compliance
    e. evidence of GCP compliance
    f. evidence of laboratory licensure requirements
    g. compliant use of select agents

h. all required representations and certifications are completed and on file.

B. Volume I – Technical Proposal Appendices

Appendices to Volume I contain supplemental data and information that should accompany the technical proposal. The combined page total of Appendices in Volume I should not exceed 70 pages unless otherwise specified in the full proposal invitation letter. Additional specific information to be included is referenced below. If a particular item is not relevant to the proposed effort, state that it is not applicable and provide a justification.

	Item	Required	Reference
1	Updated Quad Chart	Yes	Template in Attachment 6 (please note any differences with the original Quad Chart)
2	Protection of Human Subjects	If Applicable	Part IV, Section 4, paragraph B2 http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
3	Animal Welfare	If Applicable	Part IV, Section 4, paragraph B3
4	Intellectual Property	Yes	Part IV, Section 4, paragraph B4
5	Biographical Sketches	Yes	Part IV, Section 4, paragraph B5
6	Use of Select Agents	If Applicable	Part IV, Section 4, paragraph B6 http://www.cdc.gov/od/sap http://www.aphis.usda.gov/programs/ag_selectagent
7	Laboratory License Requirements	If Applicable	Part IV, Section 4, paragraph B7
8	Target Product Profile	Yes	Part IV, Section 4, paragraph B8 Template in Attachment 7
9	Supporting Data	No	Any additional product development data referenced in Volume I may be included here, provided that the Appendices remain within the 70 page limit.

B2. 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. The HHS policy on studies that involved human subjects can be accessible through the HHS website: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

B3. 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 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. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association (http://www.avma.org/resources/euthanasia.pdf). If not, present a justification for not following the recommendations.

B4. Intellectual Property

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.

B5. Biographical Sketches

Volume 1 – Technical Proposal must list the names and proposed duties of the professional personnel, consultants, and key subcontractor employees assigned to the project, and their resumes should be included in Volume 1 – Technical Proposal Appendices. 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.

B6. 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.

B7. 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.

B8. Target Product Profile

The success of a product development program requires a relentless focus on the desired characteristics of the resulting medical countermeasure product or capability. A template for a Target Product Profile is included in Attachment 7 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 is not applicable, appropriate equivalent information regarding the desired outcome of the proposed development activities should be provided.

C. Volume II – Cost Proposal

The cost proposal page limit is 50 pages and 70 pages of appended material *unless otherwise specified in the invitation* for a total of 120 pages. A Rough Order of Magnitude of costs may initially be requested and at some point, a full cost proposal will be requested. The cost proposal should contain sufficient information to allow for a meaningful evaluation. Additionally, a cost summary (not to exceed 2 pages) should be submitted in conjunction with the detailed cost proposal. The detailed costs should be classified by category (labor, materials, subcontractors, travel, etc.) and must easily link to the activities presented in Volume I – Technical Proposal, the Gantt chart/WBS, and the 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.**

Cost Proposal Cover Sheet: The following information shall be provided on the first page of your cost proposal:

1. BAA Number
2. Title of proposal
3. Development Area of Interest
4. Name and address of Offeror
5. Name and telephone number of point of contact
6. Name, address, and telephone number of Contract Administration Office, (if available)
7. Name, address, and telephone number of Audit Office (if available)
8. Proposed cost and/or price; profit or fee (as applicable); and total
9. 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.

10. Date of submission
11. Name, title and signature of authorized representative
12. 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.

Basic Cost/Price Information: The full cost proposal should contain sufficient information to allow the Government to perform a price/cost realism and a reasonableness analysis of the proposed cost or price of the work. This information should include the amounts of the line items of the proposed cost or price. The following elements by milestone event and/or proposed period of performance should be included as applicable:

i. Direct Labor- Individual labor category or person, with associated labor hours and unburdened direct labor rates;
ii. Indirect Costs – Fringe Benefits, Overhead, G&A, etc. (including base amount and rate);
iii. Travel – Separate by destinations and include number of trips, durations-number of days, number of travelers, per diem (hotel and meals in accordance with Federal Travel Regulations,), airfare, car rental, if additional miscellaneous expense is included, list description and estimated amount, etc;
iv. Subcontract – A cost proposal shall be submitted by the subcontractor. The subcontractor's cost proposal should include on company letterhead the complete company name and mailing address, technical and administrative/business point of contacts, e-mail address, and telephone number. Include the DUNS number. 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 (IV.C.) 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.
v. Consultant – Provide consultant agreement or other document which verifies the proposed loaded daily/hourly rate and labor category;
vi. Materials should be specifically itemized with costs or estimated costs. Where possible, 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,

vii. 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.

viii. Fee/profit including percentages.

A draft template for the breakdown of proposed estimated costs and labor hours is provided in Attachment 2.

The Offeror should ensure that each milestone or phase of work (base or options) includes a detailed cost budget that references the corresponding scope of work (technical activities) proposed in the SOW. The budget for each phase must align with the SOW and be presented in specific, non-severable, discrete work segments.

Salary Rate Limitation

Pursuant to current and applicable prior HHS appropriations acts, iIt 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. Volume II – Cost Proposal Appendices

The page limit for the cost proposal appendices is 70 pages, or as otherwise specified in the invitation letter. These appendices contain supplemental data of

a cost and non-cost nature that should accompany the cost proposal. Specific information to be included is referenced below. If a particular item is not relevant to the proposed effort, state that it is not applicable and provide justification.

	Item	Required	Reference
1	DUNS, TIN and NAICS	Yes	
2	Certifications and Representations	Yes	Part IV, Section 4, paragraph D2
3	CCR	Yes	
4	Security	If Applicable	Part IV, Section 4, paragraph D4 Template in Attachment 3
5	HHS Small Business Subcontracting Plan	If Applicable	Part IV, Section 4, paragraph D5
6	Summary of Related Activities	Yes	Template in Attachment 4
7	Prohibition on the Use of Appropriated Funds for Lobbying Activities [HHSAR 352.270-10]	Yes	Part IV, Section 4, paragraph D7
8	Report of Government-Owned, Contractor-Held Property	If Applicable	http://www.niaid.nih.gov/contract/forms.htm
9	Financial Capacity and Annual Financial Report	Yes	Part IV, Section 4, paragraph D9

D2. Certifications and Representations

In accordance with FAR 4.1201 prospective Offerors shall complete the Online Representations and Certifications Application (ORCA) at http://orca.bpn.gov. Offerors should make mention of its ORCA completion in its proposal and provide it "Certification Validity" period.

D3. Security

The work to be performed under this contract may involve access to sensitive BARDA program information. Therefore, the Offeror(s) may be requested to submit a written Draft Security Plan that describes their procedures and policies to defend against theft, tampering, or destruction of product-related material, equipment, documents,

information, and data. Guidance for preparing the security plan can be found in Attachment 3.

Security Plan Representative Activities may include but are not limited to:

a. The establishment of a comprehensive security program that provides a security plan for the overall protection of personnel, information, data, and facilities.
b. Security administration, as an element of the security program that address threat and risk assessments and related policies and procedures for personnel
security, physical security, information security, information technology.
c. Security management, as an element of the security program that describe each element of security: physical, operations, personnel, information, information technology, transportation; and related training, auditing, and reporting requirements.

Upon contract award, the Program Protection Officer (PPO) will review the Draft Security Plan (submitted as part of the Contractor's Cost Proposal) in detail and submit comments within ten (10) business days to the Contracting Officer (CO) to be forwarded to the Contractor. The Contractor shall review the Draft Security Plan comments, and if changes are required, submit a Final Security Plan to the U.S. Government within thirty (30) calendar days after receipt of the Program Protection Officer's (PPO) comments. The Final Security Plan shall include a timeline for compliance of all the required security measures. Upon completion of initiating all security measures, the Contractor shall supply to the Contracting Officer and Contracting Officer's Representative a letter certifying compliance to the elements outlined in the Final Security Plan. The execution of the work under this contract shall be in accordance with the approved Final Security Plan. As outlined above, the content of the Final Security Plan shall be a continuation of the Draft Security Plan submitted as part of the Contractor's Technical Proposal. **The Contractor shall ensure that the storage, generation, transmission or exchanging of BARDA sensitive information has the appropriate security controls in place.**

The following instruction/intent shall be incorporated:

> Security Reporting Requirement - Violations of established security protocols shall be reported to the Contracting Officer (CO) and Contracting Officer's Representative (COR) **within 24 hours of its discovery of any compromise, intrusion, loss or interference of its security processes and procedures. The Contractor shall ensure that all software components that are not required for the operation and maintenance of the database/control system has been removed and/or disabled. The Contractor shall provide to the CO and the COR information appropriate to Information and Information Technology software and service updates and/or workarounds to mitigate all vulnerabilities associated with the data and shall maintain the required level of system security.** 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.

D4. HHS Small Business Subcontracting Plan
Successful contract proposals that exceed $550,000, submitted by all but small business concerns, will be required to submit a satisfactory Small Business Subcontracting Plan in accordance with FAR 52.219-9.

D5. Prohibition on the Use of Appropriated Funds for Lobbying Activities [HHSAR 352.203-7]

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.

D6. Financial Capacity and 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 shall also submit a copy of the organization's most recent annual report in the cost proposal appendix.

D7. Advance Understandings
The Contracting Officer and Contractor will discuss the Contract Type during contract negotiations. A contract awarded under this BAA may utilize any number of mechanisms as appropriate, including: Cost-Reimbursement, Cost-plus-fixed-fee (CPFF), and Cost-plus-incentive-fee (CPIF), a cost sharing structure, etc. Following is a list of Contractor deliverables during the course of a contract. This list is a sample and is not intended to be all-inclusive of Contractor deliverables.

1. Invoices: Cost and Personnel Reporting, and Variances from the Negotiated Budget:
   i. The Contractor agrees to provide a detailed breakdown on invoices of the following cost categories:
      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
k. Fixed Fee
l. Total CPFF

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.

ii. 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.

2. Publications: Any manuscript or scientific meeting abstract containing data generated under this contract must be submitted to the Contracting Officer for review no less than thirty (30) calendar days for manuscripts and no less than 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.

3. Press Releases: The Contractor and all subcontractors and consultants will be required 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 BARDA 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 which are addressed above. Any press release that mentions a BARDA contract must be submitted to the Contracting Officer for review and approval no less than five (5) days prior to scheduled release.

4. Human Subjects: Research projects involving humans and/or human specimens can only be initiated with written approval by the COR.

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 Government Contracting Officer's Representative. If the Offeror fails to take such an action within the thirty (30) calendar day period, then the contract may be terminated.

5. 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).

6. 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 820, Quality System Regulation) will be the standard to be applied for manufacturing, processing, packaging, 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. The contract may be terminated if the Offeror fails to take such an action to the satisfaction of the COR within the thirty (30) calendar day period.

7. 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.

8. Identification and Disposition of Data: the Contractor will be required to provide certain data generated under this contract to 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.

9. Confidentiality of Information: The following information is covered by HHSAR Clause 352.224-70, confidentiality of Information (January 2006): Data obtained from human subjects.

10. Indemnification: The Public Readiness and Emergency Preparedness ("PREP") Act (42 USC § 247d-6d) and that Act's February 29, 2012 implementing declaration with respect to pandemic influenza vaccines (77 FR 13 329) may apply to certain activities undertaken by a Contractor under this solicitation. To the extent the PREP Act does not apply, BARDA assumes liability only to the extent provided under the Federal Tort Claims Act (28 USC Chapter 171).

11. Sharing of contract deliverables within United States Government (USG): In an effort to build a robust medical countermeasure pipeline through increased collaboration, BARDA may share technical deliverables with USG entities responsible for Medical

Countermeasure Development. In accordance with recommendations from the Public Health Emergency Medical Countermeasure Enterprise Review, agreements established in the Integrated Portfolio's Portfolio Advisory Committee (PAC) Charter, and Technology Transfer Agreements (TTA) between BARDA and the Centers for Disease Control, the Defense Threat Reduction Agency and the National Institute of Allergies and Infectious Diseases (NIAID), BARDA may share technical deliverables with federal government colleagues. This advanced understanding does not authorize BARDA to share financial information outside HHS. The Contractor is advised to review the terms of FAR Clause 52.227-14 regarding the Government's rights to deliverables submitted during performance as well as the Government's rights to data contained within those deliverables.

Section 5: Full Proposal Submission

Submit one (1) electronic copy of the Full Proposal to the e-mail address provided in invitation letter. Each volume of the proposal must be submitted as a separate and searchable Portable Document File (PDF) compatible with Adobe Acrobat version 7.0 or earlier. Each individual file shall not exceed 10 megabytes of storage space. Include the Offeror's name and the Development Area of Interest in the e-mail subject line.

In addition, mail two (2) paper copies of the Full Proposal to the following address:

Contracting Officer
Biomedical Advanced Research and Development Authority
330 Independence Ave, S.W.
Room G640
Washington, D.C. 20201

Additional copies may be requested in the Full Proposal Invitation Letter.

All Offerors will receive an e-mail acknowledging receipt of their Full Proposal.

Withdrawal of Proposals:

1. Proposal may be withdrawn by written notice received at any time before award. Withdrawals are effective upon receipt of notice by the Contracting Officer via e-mail.

2. The Government may reject Full Proposal submissions that are deemed non-compliant, i.e., that significantly deviate from the instructions in the Broad Agency Announcement or invitation to submit a Full Proposal.

Information to be requested from Successful Offerors: Offerors whose proposals are selected for potential award may be contacted to provide additional information.

Offerors that are not responsive in a timely manner to Government requests for information (defined as meeting Government deadlines established and communicated with each request) may be removed from award consideration. Offerors that submit a Full Proposal that deviates substantially from their Quad Chart and White Paper 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.

All proposals are treated as privileged 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 contained FAR 52.215-1(e) '*Restrictions on disclosure and use of data.'*

Section 6: General Information

CLASSIFIED SUBMISSIONS: Classified proposals will not be accepted.

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 e-mailed to FLU-BAA@hhs.gov prior to expending time and effort in preparing a proposal. The appropriate BARDA personnel will discuss with any conflict of interest with prospective Offeror.

UNSUCCESSFUL PROPOSAL DISPOSITION: Unless noted in an Offeror's proposal to the contrary, unsuccessful Full Proposals will be retained for six (6) months from declination and then properly destroyed.

Part V: Quad Chart, White Paper, and Full Proposal Evaluation

A. Quad Chart and White Paper Evaluation Criteria:

The decision to invite an Offeror to submit a Full Proposal will be based on an evaluation of each Offeror's Quad Chart and White Paper. The Quad Chart and White Paper will be evaluated by a scientific review process based on the following criteria that are listed in descending order of importance pursuant to FAR 35.016. The sub-criteria listed under each criterion are of equal importance to each other.

a. **Program Relevance**

1. Medical countermeasures that address the priorities outlined in Part I: Development Areas of Interest.
2. Medical countermeasures, devices and diagnostics that align with the objectives outlined in the *National Strategy for Pandemic Influenza,* the *HHS Pandemic Influenza Implementation Plan*, the *BARDA Strategic Plan*, and other Federal Government strategy documents.
3. The maturity of the proposed product as determined by TRL criteria in Attachment 1, and as required for each Development Area of Interest. Technological maturity should be justified by the inclusion of relevant data in the white paper.
4. 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. **Scientific and Technical Merit**

1. The feasibility of the proposed plans and methods to successfully complete the proposed development activity.
2. The Offeror's understanding of the scope of the proposed activity and the technical effort needed to address it.
3. The reasonableness of the proposed schedule.
4. The Offeror's understanding of the statutory and regulatory requirements for FDA licensure/approval.
5. The Offeror's freedom to operate given the intellectual property status of the proposed technology.

B. Full Proposal Evaluation Criteria:

Pursuant to FAR 35.016, the Full Proposal will be evaluated by a peer or scientific review process based on the following criteria that are in descending order of importance.

1. Technical Proposal Evaluation Criteria:

The Technical Proposal will be evaluated based on the following criteria that are listed in descending order of importance. The sub-criteria listed under each criterion are of equal importance to each other.

a. **Program Relevance**

1. Medical countermeasures that address the priorities outlined in Part I: Development Areas of Interest.

2. Medical countermeasures, devices and diagnostics that align with the objectives outlined in the *National Strategy for Pandemic Influenza,* the *HHS Pandemic Influenza Implementation Plan*, the *BARDA Strategic Plan,* and other Federal Government strategy documents
3. The maturity level of the proposed product as determined by TRL criteria in Attachment 1, and as required for each Development Area of Interest. Technological maturity should be justified by the inclusion of relevant data in the technical proposal.
4. 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. **Scientific and Technical Merit**

1. The feasibility and validity of the proposed plans and technical methods to successfully complete the proposed development activity.
2. The Offeror's understanding of the scope of the proposed activity and the technical effort needed to address it.
3. The reasonableness of the proposed schedule.
4. The Offeror's understanding of the statutory and regulatory requirements for FDA licensure/approval.
5. The Offeror's freedom to operate given the intellectual property status of the proposed technology.

c. **Capabilities, Experience, and Key Personnel**

1. The Offeror's ability to manage the proposed effort, and to avoid interference with other current projects.
2. The expertise of technical personnel proposed.
3. The Offeror's experience in relevant efforts with similar resources.
4. The necessary facilities and infrastructure to carry out the proposed effort (may be fulfilled through subcontractors and other partners).
5. An organizational chart of the offeror's personnel.

2. Past Performance Evaluation Criteria:

a. Past performance information will be evaluated to the extent of determining the Offeror's ability to perform the contract successfully.

b. The Government is not required to contact all references provided by the Offeror. References other than those identified by the Offeror may be contacted by the Government to obtain additional information that may be used in the evaluation of the Offeror's past performance.

3. Cost Proposal Evaluation Criteria:

a. Cost realism and reasonableness. Each price/cost response will be reviewed for price/cost realism, reasonableness, and overall best value to the Government. Members of the review team may presume that the technical approach provided by the Offeror serves as a rationale for the labor mix and labor hours used.

b. 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.

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

C. Categorization:

The Full Proposal will be evaluated and categorized as follows:

CATEGORY I: Well conceived, scientifically, and technically sound proposals important to program goals and objectives. Minor modifications to the technical and cost proposals may be necessary prior to contract award. Proposals in Category I are recommended for negotiation and possible acceptance, subject to a successful negotiation process and availability of funds.

CATEGORY II: Scientifically and technically viable proposals with the potential to advance program goals and objectives. However, additional supporting information and/or written revisions are necessary prior to final evaluation of the proposal. Once the additional information and/or revisions are provided by the Offeror, a technical review will be required to determine whether the final classification of the Full Proposal will be Category I or Category III.

CATEGORY III: Proposals that are not technically sound or do not meet program goals and objectives. Category III proposals will not be considered for award.

Offerors selected for negotiation 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 Project Officer in coordination with the Contracting Officer. 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.

D. Full Proposal Award Decision:

The final Full Proposal evaluation will be based on an assessment of the overall best value to the Government based on the above evaluation criteria. Awards, if any, will be based on the Full Proposal evaluation, funds availability, and other programmatic

considerations. Award is also dependent upon demonstration by the applicant that they have adequately addressed the following requirements:

a. Research involving Human Subjects/Anatomical Substances (if proposed).
b. Research involving Animals (if proposed).
c. Evidence of GLP Compliance (if appropriate).
d. Evidence of GMP Compliance (if appropriate).
e. Evidence of GCP Compliance (if appropriate).
f. Evidence of Laboratory Licensure Requirements (if appropriate)
g. Compliant Use of Select Agents (if appropriate)
h. All required Representations and Certifications are completed and on file.

Part VI: Special Instructions

Special instructions will be posted to this BAA as necessary. Please monitor https://www.fbo.gov for updates.

Part VII: Attachments

Attachment 1: Technology Readiness Level Criteria

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

Attachment 1A: Draft Technology Readiness Level Definitions for Medical In-Vitro Diagnostic Devices, may be used for Area of Interest 3: Clinical Influenza Test Systems and Diagnostic Tools.

Attachment 1B: Department of Defense Technology Readiness Assessment Deskbook, Appendix E. Biomedical Technology Readiness Levels (TRLs) may be used for Area of Interest 1: Personal Protective Equipment for Influenza Infection & All-Hazards, Area of Interest 2: Full-Featured Continuous Ventilators for Influenza Infection & All-Hazards, and Area of Interest 3: Clinical Influenza Test Systems and Diagnostic Tools.

Attachment 1C: Technology Readiness Levels for Medical Countermeasure Products (Drugs and Biologics) may be used for Area of Interest 4: Influenza Therapeutics and Area of Interest 5: Influenza Vaccines.

Offerors applying for Area of Interest 3: Clinical Influenza Test Systems and Diagnostic Tools may use Attachments 1A or 1B to evaluate the maturity of their technology.

Attachment 1A: Draft Technology Readiness Level (TRL)
Definitions for Medical In-Vitro Diagnostic Devices

FOR USE WITH AREA OF INTEREST 3

Notice: This document does not serve as official FDA Guidance nor does it represent the Agency's current thinking on this topic. For the purposes of a regulatory application seeking licensure/approval, additional data may be required by FDA.

TRL 1 Basic Research
Generation of scientific knowledge of fundamental phenomena. Findings are peer reviewed and serve as foundation for new technologies.
Decision Criteria: Literature reviews, market surveys, White Papers.

TRL 2 Basic Invention
Intense focus on experimental designs for possible application of scientific approach to a specific problem.
Decision Criteria: Hypothesis-based research and development efforts. Research plans and protocols are developed, peer-reviewed, and approved for funding. Design controls instituted.

TRL 3 Initial Validation of Analytical Components
Basic hypothesis-based research, data collection analysis to test hypothesis and explore alternatives. Initial test of design concepts. Critical components defined and tested independently (the term component is defined in 820.3(c)). Product design and development plan drafted.
Decision Criteria: Initial proof of concept for device demonstrated in a limited number of laboratory experiments; may use surrogate or spiked samples.

TRL 4 Transition from Research to Development
Non-GLP research to define parametric data required for assessment. Initial specifications for device, systems, and subsystems determined. Device evaluation at in-house laboratories. Procedures and methods to be used during non-clinical, pre-clinical, and clinical studies in evaluating devices and systems are identified. Potential safety problems identified through risk analysis. Ad hoc hardware in a laboratory. Basic software as applicable.
Decision Criteria: Proof of concept demonstrated for devices with laboratory procedures defined. Feasibility data collected to identify a diagnostic target or signal that will be of value in diagnosis of biothreat agents.

AT THIS POINT (IF NOT SOONER), THE FDA SHOULD BE CONTACTED FOR PRE-IDE (INVESTIGATIONAL DEVICE EXEMPTION) MEETINGS TO DISCUSS PRDUCT INTENDED USE, ANALYTICAL/CLIICAL STUDY DESIGNS AND REGULATORY STRATEGY RE: NEED FOR AN IDE, PRE-MARKET APPLICATION (PMA OR 510K), AND PRODUCT DEVELOPMENT PROTOCOLS (PDP)

TRL 5 Product Development/ Begin Design Controls

Assessment of existing diagnostic modalities and how the new device relates to these other approaches. Intended use and indications for use defined. Tissue, organ, or body fluid spiked samples are evaluated. Suppliers and service providers qualified and type and extent of control defined. Purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use defined and balanced. Components integrated and tested as systems and subsystems.

Decision Criteria: Devices tested through simulations. Pre-IDE submitted to and reviewed by FDA–CDRH to determine if analytical and clinical evaluations proposed are appropriate for intended use.

TRL 6 Pre-Clinical / In-House Testing

Demonstrate analytical and functional characteristics of the device in a controlled laboratory setting, and initiate testing on appropriate clinical samples. Initiate validation master plan for critical processes and prepare final assembly of components. Manufacturing personnel participate in the design process up front to facilitate transfer of design to manufacturing.

Candidate Diagnostic Device: Analytical performance assessed (including analytical sensitivity, in-house precision, and analytical specificity) by testing real or simulated samples of interest.

IDE Ready: A full package, including the clinical evaluation protocol, is prepared for submission to the FDA (if a significant risk device study), for submission to an IRB (if a non-significant risk device study), or for submission to an IRB (if waived according to FDA exemptions from IDE requirements 812.2(c)(3)).

Decision Criteria: Evidence supports proceeding to pre-clinical studies.

TRL 7 Investigational Phase

Functional and pre-clinical testing begun with fully integrated device (systems and subsystems). Manufacturing process is validated and initial production units used for final design verification and validation activities. Continued interactions with FDA-CDRH.

Decision Criteria: Pre-clinical and functional testing completed. Design verification completed for the final product. Initial commercial scale devices are produced; release criteria established. Preliminary data collected and presented and discussed with CDRH. IDE submitted and approved by FDA-CDRH as applicable (21 CFR Part 812).

TRL 8 End of System Development; Use in Actual Setting with Clinical Samples

Clinical evaluations implemented for assessing diagnostic accuracy of device for its intended use. Risk/benefit for use of device is assessed. Data in support of product labeling for directions-for-use is established; any needed lot consistency/reproducibility studies completed. Design locked final review and approval prior to final transfer to manufacturing. Pre-Market Approval (PMA) and/or 510(k) application to FDA-CDRH submitted.

Decision Criteria: Approval of the PMA or as applicable clearance of the 510(k) by FDA-CDRH.

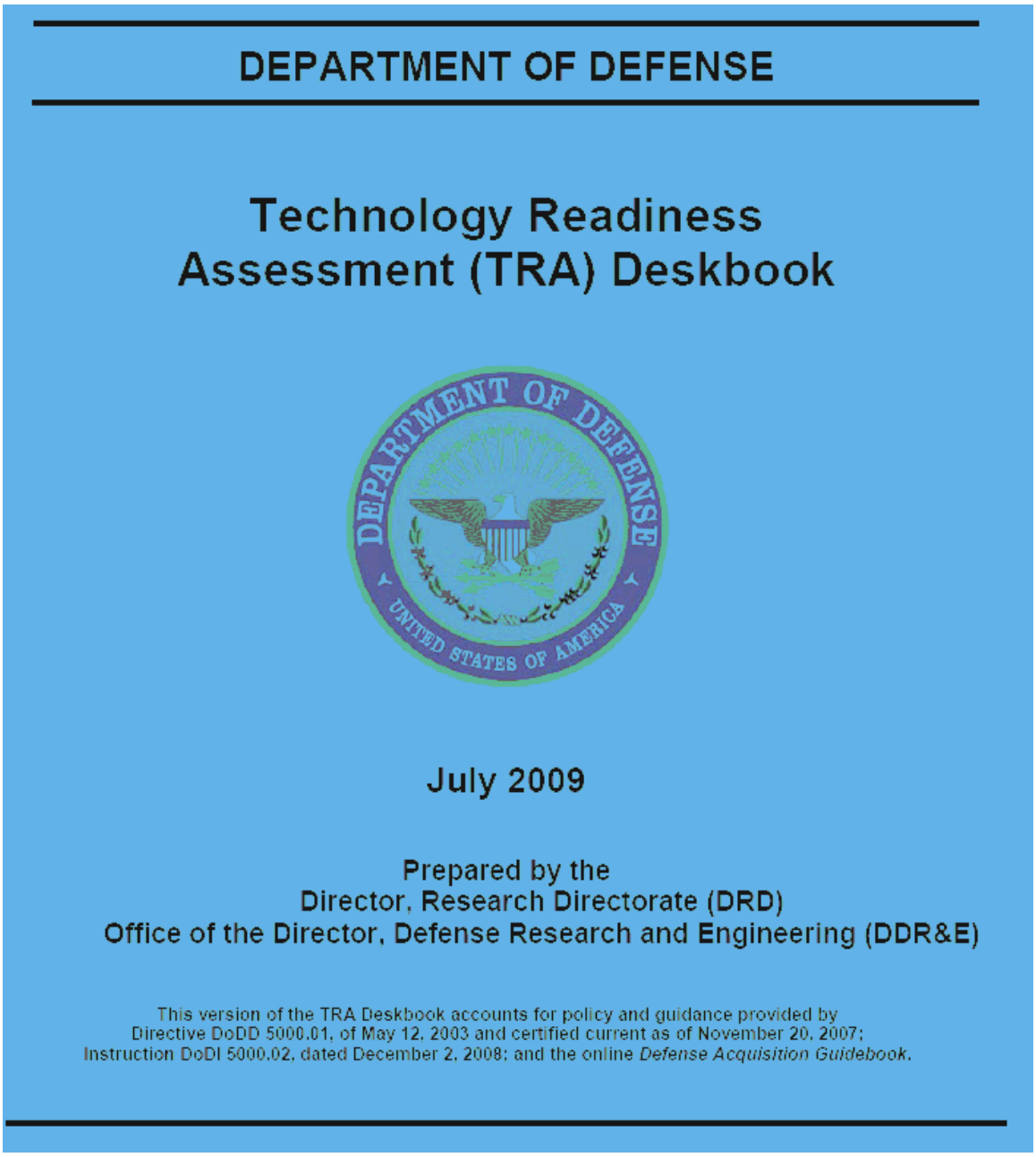
TRL 9 Data	**Used in Clinical Settings with Clinical Samples, Post-Market Studies or Collection as applicable** When appropriate, post-marketing surveillance data collection studies to monitor device performance under broader conditions for use. *Decision Criteria:* None - continued surveillance. Corrective and Preventive Action Program to monitor performance.

Attachment 1B: Department of Defense Technology Readiness Assessment Deskbook

FOR USE WITH AREAS OF INTEREST 1, 2 and 3

The entire TRA Handbook can be accessed at:
http://www.dod.mil/ddre/doc/DoD_TRA_July_2009_Read_Version.pdf
(verified 3/12/2012)

TRA Deskbook, Appendix E. Biomedical Technology Readiness Levels, Pages E3-E26:



DEPARTMENT OF DEFENSE

Technology Readiness Assessment (TRA) Deskbook

July 2009

Prepared by the
Director, Research Directorate (DRD)
Office of the Director, Defense Research and Engineering (DDR&E)

This version of the TRA Deskbook accounts for policy and guidance provided by Directive DoDD 5000.01, of May 12, 2003 and certified current as of November 20, 2007; Instruction DoDI 5000.02, dated December 2, 2008; and the online *Defense Acquisition Guidebook*.

Biomedical Technology Readiness Levels (TRLs)

Note: *Medical-related items require Technology Readiness Level (TRL) definitions and descriptions that are appropriate to the technologies upon which they are based and that account for the statues and regulations that govern their development and use. In recognition of these factors, the United States Army Medical Research and Materiel Command (USAMRMC) took the initiative to establish appropriate definitions, descriptions, and processes in the context of military medical research and development (R&D) and Food and Drug administration (FDA) statutory and regulatory requirements. This appendix provides the results of their effort.*

E.1 Background

Department of Defense (DoD) policy mandates the use of U.S. FDA-approved products for force health protection,[1] and the USAMRMC has always adhered to the regulatory requirements of the FDA for its studies of drugs, biologics, and devices in humans. To ensure compliance with the clinical phases of the FDA-regulated process and to reduce technological risk, the USAMRMC developed and recently updated their general guidelines for assigning TRLs to drug, vaccine, and medical device development programs.[2] These guidelines are not considered absolutes, and characterization of activities associated with TRLs can and does vary at times.

The science and technology (S&T) and acquisition program managers (PMs) work together in exercising discretion in the selection, progression, and timing of specific activities to be accomplished in the attainment of particular TRLs. Such flexibility and tailoring are needed to align the TRL decision criteria appropriately with the maturation and risk characteristics of a particular technology, including consideration of the associated investment strategy and transition procedures that may vary among PMs.

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1 For example, Department of Defense Directive (DoDD) 6200.2, *Use of Investigational New Drugs for Force Health Protection,* August 1, 2000, or Health Affairs Policy 95-011, *Tri-Service Pharmacy Policy Guidance,* July 26, 1995.

2 *Biomedical Technology Readiness Levels (TRLs)*, prepared for the Commander, U.S. Army Medical Research and Materiel Command, under Contract DAMD17-98-D-0022, Science Applications International Corporation, 3 June 2003.

When transitioning from technology development to product development, the risks are greater if the TRL of a Critical Technology Element (CTE) is low. For medical technologies, risk reduction is not linear across TRLs. The rate of risk reduction remains very low until very late. Historically, FDA-regulated products, such as vaccines, do not achieve significant risk reduction (i.e., greater than 50%) until completion of Phase 3 clinical trials and approval of a biologics license application by the FDA (TRL 8). Industry's experience is that only one in four vaccines going into Phase 3 trials is licensed. Similarly, whereas technology maturation is commonly perceived as a sequential continuum of activities from basic research, through development, to production and deployment, the evolution of the TRL for a biomedical CTE may not be sequential, especially in those cases where FDA anchors are undefined. In cases of success or failure, the incremental change in the level of technology readiness may be greater than a single TRL. For example, upon successful completion of a pivotal study, biomedical information readiness levels may move from TRL 3 or 4 to TRL 9.

Biomedical TRL descriptions provide a systematic way for the S&T community to assess and communicate to the Milestone Decision Authority (MDA) the maturity level of a particular technology or combination of technologies and the maturity necessary for successful product development. This appendix provides equivalent TRL descriptions applicable to biomedical technologies in four categories:

1. Pharmaceutical (i.e., drugs)
2. Pharmaceutical (i.e., biologics/vaccines)
3. Medical Devices
4. Medical Information Management/Information Technology (IM/IT) and Medical Informatics.

The TRLs for the first three categories have been developed from the DoD's generic definitions, the applicable FDA regulatory process, and industry practices and experience with its R&D processes (discovery through manufacturing, production, and marketing). The last category includes elements of formal regulatory processes and logical events in deriving comparable levels of maturity. Wherever practical, the USAMRMC intends to use external anchors such as "FDA events" to define each TRL decision criterion. Furthermore, activities described as occurring between successive TRL decision criteria are intended to exemplify the kinds of activities that routinely take place when maturation is sequential and stepwise. However, these examples are neither mandatory nor all inclusive.

Figure E-1 and Table E-1 build upon this work by providing examples of supporting information and documentation required to support the assignment of TRLs as the program progresses.

The proponent for this document is the **Deputy for Research and Development: Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZA, 504 Scott Street, Fort Detrick, MD 21702-5012.**

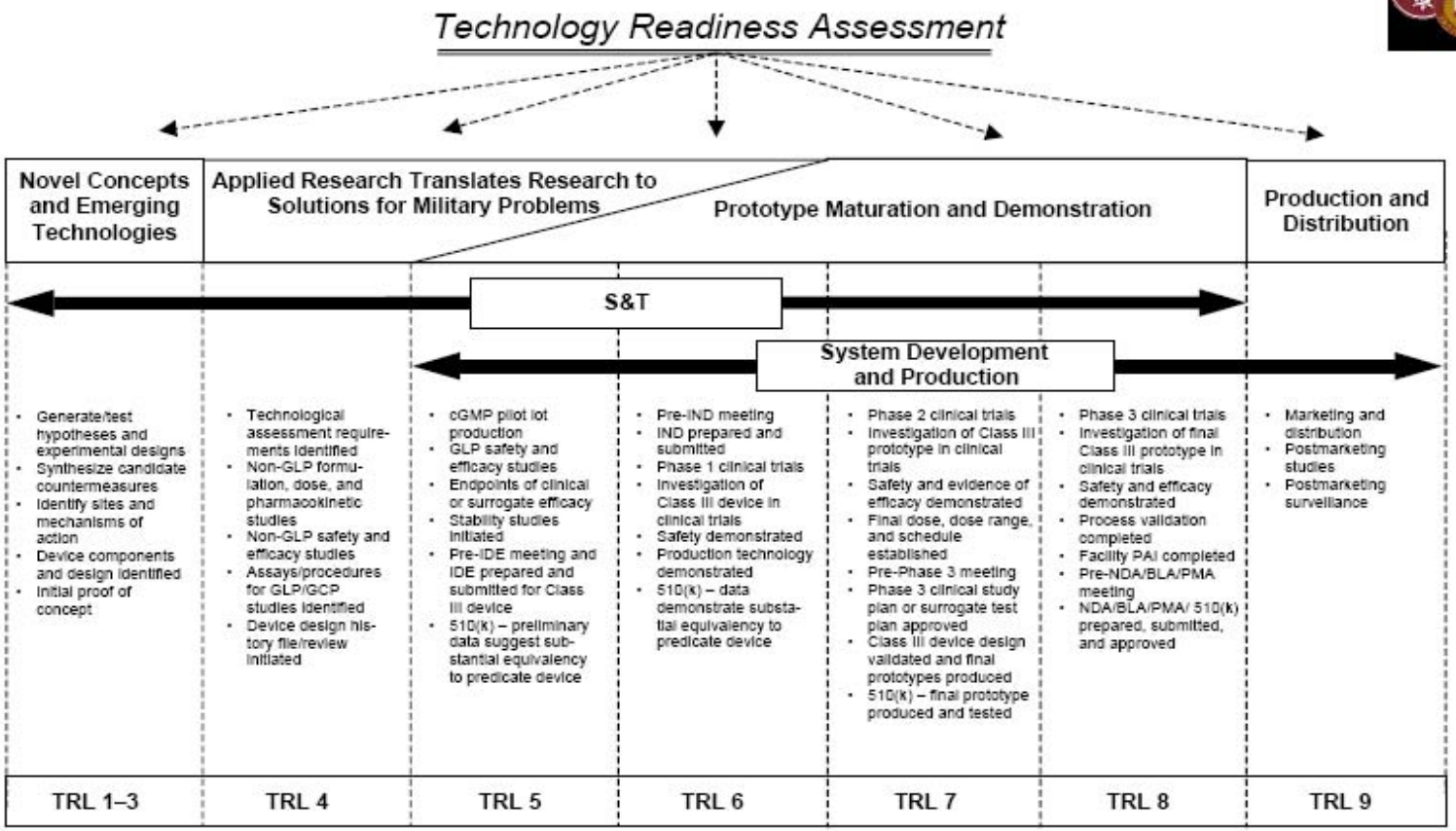

Figure E-1. TRLs in the Medical Materiel Regulatory Process

Note for Figure E-1: *The TRL descriptions are not considered absolutes, and characterization of activities associated with TRLs can and does vary at times. The S&T and acquisition PMs work together in exercising discretion in the selection, progression, and timing of specific activities to be accomplished, particularly with regard to TRL 5. Such flexibility and tailoring are needed to align the TRL decision criteria appropriately with maturation and risk characteristics of a particular technology, including consideration of the associated investment strategy and transition procedures that may vary among PMs.*

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General Note for Table E-1: *The N1, N2, N3, and N4 superscripts refer to the Notes that are listed at the end of Table E-1.*

Table E-1. Proposed TRLs for Medical Research, Development, Test, and Evaluation (RDT&E)

TRL 1 National Aeronautics and Space Administration (NASA)/*Defense Acquisition Guidebook*[3] TRL Definition: Basic principles observed and reported				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)**[N1, N2]	**Medical Devices**[N3, N4]	**Medical IM/IT & Medical Informatics**
Lowest level of technology readiness. Scientific research begins to be translated into applied research and development. Examples might include paper studies of a technology's basic properties.	Lowest level of technology readiness. Maintenance of scientific awareness and generation of scientific and bioengineering knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies.	Lowest level of technology readiness. Maintenance of scientific awareness and generation of scientific and bioengineering knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies.	Lowest level of technology readiness. Maintenance of scientific awareness and generation of scientific and bioengineering knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies.	Hardware/software (HW/SW) system technology explored. Basic theories applied to IM/IT field suggesting promise.
	TRL 1 Decision Criterion: Scientific literature reviews and initial market surveys are initiated and assessed. Potential scientific application to defined problems is articulated.	**TRL 1 Decision Criterion:** Scientific literature reviews and initial market surveys are initiated and assessed. Potential scientific application to defined problems is articulated.	**TRL 1 Decision Criterion:** Scientific literature reviews and initial market surveys are initiated and assessed. Potential scientific application to defined problems is articulated.	**TRL 1 Decision Criterion:** Identification of the potential medical solution to mission need. Medical Informatics data and knowledge representation issues are defined.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	Reviews of open, published scientific literature concerning basic principles. Findings from market surveys of the open literature. **Note:** *Privately funded research findings or market surveys are proprietary and rarely available to the public.*	Reviews of open, published scientific literature concerning basic principles. Findings from market surveys of the open literature. **Note:** *Privately funded research findings or market surveys are proprietary and rarely available to the public.*	Reviews of open, published scientific literature concerning basic principles. Findings from market surveys of the open literature. **Note:** *Privately funded research findings or market surveys are proprietary and rarely available to the public.*	

[3] The *Defense Acquisition Guidebook* (in revision) contains non-mandatory guidance on best practices, lessons learned, and expectations.

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 2 NASA/*Defense Acquisition Guidebook* TRL Definition: Technology concept and/or application formulated				
NASA/ *Defense Acquisition Guidebook* TRL Description	*USAMRMC Equivalent TRL Descriptions*			
	Pharmaceutical (Drugs)[N1, N2]	Pharmaceutical (Biologics, Vaccines)[N1, N2]	Medical Devices[N3, N4]	Medical IM/IT & Medical Informatics
Invention begins. Once basic principles are observed, practical applications can be invented. Applications are speculative, and there may be no proof or detailed analysis to support the assumptions. Examples are limited to analytic studies.	Intense intellectual focus on the problem, with generation of scientific "paper studies" that review and generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues.	Intense intellectual focus on the problem, with generation of scientific "paper studies" that review and generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues.	Intense intellectual focus on the problem, with generation of scientific "paper studies" that review and generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues.	HW/SW system invention begins. Overall system concepts are documented by flowcharting or other system-descriptive techniques.
	TRL 2 Decision Criterion: Hypothesis(es) is generated. Research plans and/or protocols are developed, peer reviewed, and approved.	**TRL 2 Decision Criterion:** Hypothesis(es) is generated. Research plans and/or protocols are developed, peer reviewed, and approved.	**TRL 2 Decision Criterion:** Hypothesis(es) is generated. Research plans and/or protocols are developed, peer reviewed, and approved.	**TRL 2 Decision Criterion:** Identification of the potential medical solution to mission need. Medical Informatics data and knowledge representation issues are defined.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	Focused literature reviews are conducted and scientific discussions are held to generate research plans and studies that identify potential targets of opportunity for therapeutic intervention and to facilitate strategic planning. Supporting analyses provide scientific information and data for developing research proposals for filling in data gaps and identifying candidate concepts and/or therapeutic drugs. Documented by peer-reviewed approved protocol(s) or research plan(s).	Focused literature reviews are conducted and scientific discussions are held to generate research plans and studies that identify potential targets of opportunity for therapeutic intervention and to facilitate strategic planning. Supporting analyses provide scientific information and data for developing research proposals for filling in data gaps and identifying candidate concepts and/or therapeutic drugs. Documented by peer-reviewed approved protocol(s) or research plan(s).	Focused literature reviews are conducted and scientific discussions are held to generate research plans and studies that identify potential targets of opportunity for therapeutic intervention and to facilitate strategic planning. Supporting analyses provide scientific information and data for developing research proposals for filling in data gaps and identifying candidate concepts and/or devices. Documented by peer-reviewed approved protocol(s) or research plan(s).	

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 3 NASA/*Defense Acquisition Guidebook* **TRL Definition:** Analytical and experimental critical function and/or characteristic proof-of-concept				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)[N1, N2]**	**Medical Devices[N3, N4]**	**Medical IM/IT & Medical Informatics**
Active research and development is initiated. This includes analytical studies and laboratory studies to physically validate analytical predictions of separate elements of the technology. Examples include components that are not yet integrated or representative.	Basic research, data collection, and analysis begin in order to test the hypothesis, explore alternative concepts, and identify and evaluate technologies supporting drug development. Initial synthesis of countermeasure candidate(s) and identification of their sites and mechanisms of action. Initial characterization of candidates in preclinical studies.	Basic research, data collection, and analysis begin in order to test hypothesis, explore alternative concepts, and identify and evaluate critical technologies and components supporting candidate biologic/vaccine constructs research and eventual development of a candidate countermeasure. Agent challenge studies are conducted to support models based on presumed battlefield conditions. Research-scale process initiation and evaluation is conducted, as are studies to identify site(s) and mechanism(s) of action, potential correlates of protection for vaccines, and initial physical/chemical characterization of constructs.	Basic research, data collection, and analysis begin in order to test hypothesis, explore alternative concepts, and identify and evaluate component technologies. Initial tests of design concept and evaluation of candidate(s). Study endpoints defined. Animal models (if any) are proposed. Design verification, critical component specifications, and tests (if a system component or necessary for device test and evaluation (T&E)).	Separate elements of HW/SW system components are investigated and developed but not yet integrated or representative.
	TRL 3 Decision Criterion: Initial proof-of-concept for candidate drug constructs is demonstrated in a limited number of *in vitro* and *in vivo* research models.	**TRL 3 Decision Criterion:** Initial proof-of-concept for biologic/vaccine constructs is demonstrated in a limited number of *in vitro* and *in vivo* research models.	**TRL 3 Decision Criterion:** Initial proof-of-concept for device candidates is demonstrated in a limited number of laboratory models (may include animal studies).	**TRL 3 Decision Criterion:** Medical Informatics data and knowledge representation schema are modeled.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	Documentation of the results of laboratory studies demonstrates preliminary proof-of-concept in *in vitro* and animal studies.	Documentation of the results of laboratory studies demonstrates preliminary proof-of-concept with candidate biologic/vaccine constructs in *in vitro* and animal studies.	Documentation of the results of laboratory studies demonstrates preliminary proof-of-concept in laboratory models.	

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 4 NASA/*Defense Acquisition Guidebook* TRL Definition: Component and/or breadboard validation in laboratory environment				
NASA/ *Defense Acquisition Guidebook* TRL Description	*USAMRMC Equivalent TRL Descriptions*			
	Pharmaceutical (Drugs)[N1, N2]	Pharmaceutical (Biologics, Vaccines)[N1, N2]	Medical Devices[N3, N4]	Medical IM/IT & Medical Informatics
Basic technological components are integrated to establish that they will work together. This is relatively "low fidelity" compared to the eventual system. Examples include integration of "ad hoc" hardware in the laboratory.	Non-Good Laboratory Practice (GLP) laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous (worst case) experimental design. Exploratory study of candidate drugs (e.g., formulation, route(s) of administration, method of synthesis, physical/chemical properties, metabolic fate and excretion or elimination, and dose ranging)). Candidate drugs are evaluated in animal model(s) to identify and assess potential safety and toxicity problems, adverse events, and side effects. Assays to be used during non-clinical and clinical studies in evaluating candidate drugs are identified.	Non-GLP laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous (worst case) experimental design. Exploratory study of critical technologies for effective integration into candidate biologic/vaccine constructs (e.g., environmental milieu (pH, adjuvant, stabilizers and preservatives, buffers, and so forth), route(s)/ methods of administration, proposed production/ purification methods, further physical/chemical characterization, metabolic fate and excretion or elimination, dose ranging, and agent challenge studies for protection)). Candidate biologic/vaccine constructs are evaluated in animal model(s) to identify and assess safety and toxicity, biological effects, adverse effects, and side effects. Assays, surrogate markers, and endpoints to be used during non-clinical and clinical studies to evaluate and characterize candidate biologic/vaccine constructs are identified.	Non-GLP laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous (worst case) experimental design. Exploratory study of candidate device(s)/systems (e.g., initial specification of device, system, and subsystems). Candidate devices/systems are evaluated in laboratory and/or animal models to identify and assess potential safety problems, adverse events, and side effects. Procedures and methods to be used during non-clinical and clinical studies in evaluating candidate devices/systems are identified. The design history file, design review, and, when required, a Device Master Record (DMR), are initiated to support either a 510(k)[4] or Premarket Approval (PMA).	Prototype produced. HW/SW system components are integrated to establish that the pieces will work together. This is relatively "low fidelity" compared to the eventual system.
	TRL 4 Decision: Criterion: Proof-of-concept and safety of candidate drug formulation(s) are demonstrated in defined laboratory/animal model(s).	**TRL 4 Decision Criterion:** Proof-of-concept and safety of candidate biologic/vaccine constructs are demonstrated in defined laboratory/animal model(s).	**TRL 4 Decision Criterion:** Proof-of-concept and safety of candidate devices/systems are demonstrated in defined laboratory/animal models.	**TRL 4 Decision Criterion:** Medical Informatics data and knowledge representation models are instantiated with representative data or knowledge from applicable domain.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	Documented proof-of-concept and safety of candidate drug formulations are demonstrated by results of formulation studies, laboratory tests, pharmacokinetic studies, and selection of laboratory/animal models.	Documented proof-of-concept and safety of candidate biologics/vaccines are demonstrated by results of proposed production/purification methods, laboratory tests, pharmocokinetic studies, and selection of laboratory/animal models.	Reviewers confirm proof-of-concept and safety of candidate devices/systems from laboratory test results, laboratory/animal models, and documentation of the initial design history file, design review, and, when required, a DMR. The documented initial design history file, design review, and, when required, a DMR support either a 510(k) or PMA.	

[4] A 510(k) is a premarket notification for medical devices.

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 5 NASA/*Defense Acquisition Guidebook* **TRL Definition:** Component and/or breadboard validation in a relevant environment				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)[N1, N2]**	**Medical Devices[N3, N4]**	**Medical IM/IT & Medical Informatics**
Fidelity of breadboard technology increases significantly. The basic technological components are integrated with reasonably realistic supporting elements so they can be tested in a simulated environment. Examples include "high-fidelity" laboratory integration of components.	Intense period of non-clinical and preclinical research studies involving parametric data collection and analysis in well-defined systems, with pilot lots of candidate pharmaceuticals produced and further development of selected candidate(s). Results of research with pilot lots provide basis for a manufacturing process amenable to current Good Manufacturing Practice (cGMP)-compliant pilot lot production. Conduct GLP safety and toxicity studies in animal model systems. Identify endpoints of clinical efficacy or its surrogate. Conduct studies to evaluate the pharmacokinetics and pharmacodynamics of candidate drugs. Stability studies initiated.	Intense period of non-clinical and preclinical research studies involving parametric data collection and analysis in well-defined systems with pilot lots of candidate biologics/vaccines produced and further development of selected candidates. Research results support proposing a potency assay, proposing a manufacturing process amenable to cGMP-compliant pilot lot production, identifying and demonstrating proof-of-concept for a surrogate efficacy marker in an animal model(s) applicable to predicting protective immunity in humans, and demonstrating preliminary safety and efficacy against an aerosol challenge in a relevant animal model. Conduct GLP safety and toxicity studies in animal model systems. Identify endpoints of clinical efficacy or its surrogate in animal models that may be applicable to predicting protective immunity in humans. Conduct studies to evaluate immunogenicity, as well as pharmacokinetics and pharmacodynamics when appropriate. Stability studies initiated.	Further development of selected candidate(s). Devices compared to existing modalities and indications for use and equivalency demonstrated in model systems. Examples include devices tested through simulation, in tissue or organ models, or animal models if required. All component suppliers/vendors are identified and qualified; vendors for critical components are audited for cGMP/Quality System Regulation (QSR) compliance. Component tests, component drawings, design history file, design review, and any DME are verified. Product Development Plan is drafted. Pre-Investigational Device Exemption (IDE) meeting is held with Center for Devices and Radiological Health (CDRH) for proposed Class III devices, and the IDE is prepared and submitted to CDRH. For a 510(k), determine substantially equivalent devices and their classification, validate functioning model, ensure initial testing is complete, and validate data and readiness for cGMP inspection.	First technical test of prototype. HW/SW system components are integrated, and realistic supporting elements are employed so that the system can be tested in a simulated environment. Actual interfaces to supporting systems are specified and development begins.
	TRL 5 Decision Criterion: A decision point is reached at which it is determined that sufficient data on the candidate drug exist in the draft technical data package to justify proceeding with preparation of an Investigational New Drug (IND) application.	**TRL 5 Decision Criterion:** A decision point is reached at which it is determined that sufficient data on the candidate biologic/vaccine exist in the draft technical data package to justify proceeding with preparation of an IND application.	**TRL 5 Decision Criterion:** IDE review by CDRH results to determine if the investigation can begin. For a 510(k), preliminary findings suggest the device will be substantially equivalent to a predicate device.	**TRL 5 Decision Criterion:** Medical Informatics data and knowledge representation models are implemented as data and/or knowledge management systems and tested in a laboratory environment.

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 5 NASA/*Design Acquisition Guidebook* TRL Definition: Component and/or breadboard validation in a relevant environment (Continued)				
	Pharmaceutical (Drugs)[N1, N2]	Pharmaceutical (Biologics, Vaccines)[N1, N2]	Medical Devices[N3, N4]	
	Supporting Information	Supporting Information	Supporting Information	
	Reviewers confirm adequacy of information and data on candidate drug in a draft technical data package to support preparation of IND application. Documentation in the draft technical data package contains data from animal pharmacology and toxicology studies, proposed manufacturing information, and clinical protocols for Phase 1 clinical testing.	Reviewers confirm adequacy of information and data on candidate biologic/vaccine constructs in draft technical data package to support preparation of an IND application. Documentation in the draft technical data package contains data from animal pharmacology and toxicology studies, proposed manufacturing information, and clinical protocols suitable for Phase 1 clinical testing.	For investigation of a Class III device to begin in humans, the following are needed: (1) the FDA's and sponsor's summary minutes of pre-IDE meeting document agreements and general adequacy of information and data to support preparation and submission of IDE application and (2) an FDA letter acknowledging receipt of IDE by CDRH. The investigational plan (clinical trials) can begin after 30 days (barring a clinical hold from the FDA) or sooner if CDRH approves the IDE within 30 days. In the latter case, CDRH will provide written notification. The submitted IDE includes information regarding the sponsor, intended use of device, rationale for use of device, investigational plan, instructions for use of device, labeling, and informed consent. For a 510(k) device, reviewers confirm preliminary claim that the medical device appears substantially equivalent to a predicate device, the proposed classification is consistent with 21CFR860, there is a functioning model, and testing results support substantial equivalency.	

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 6 NASA/*Defense Acquisition Guidebook* **TRL Definition:** System/subsystem model or prototype demonstration in a relevant environment				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)[N1, N2]**	**Medical Devices[N3, N4]**	**Medical IM/IT & Medical Informatics**
Representative model or prototype system, which is well beyond that of TRL 5, is tested in a relevant environment. Represents a major step up in a technology's demonstrated readiness. Examples include testing a prototype in a high-fidelity laboratory environment or in a simulated operational environment.	Pre-IND meeting (Type B) held with the Center for Drug Evaluation and Research (CDER). IND application is prepared and submitted. Phase 1 clinical trials are conducted to demonstrate safety of candidate in a small number of humans under carefully controlled and intensely monitored clinical conditions. Evaluation of pharmacokinetic and pharmacodynamic data to support the design of well-controlled, scientifically valid Phase 2 studies. Production technologies are demonstrated through production-scale cGMP plant qualification.	Pre-IND meeting (Type B) held with the Center for Biologics Evaluation and Research (CBER). IND application is prepared and submitted. Phase 1 clinical trials are conducted to demonstrate safety of candidates in a small number of subjects under carefully controlled and intensely monitored clinical conditions. Evaluation of immunogenicity and/or pharmacokinetics and pharmacodynamics data to support design of Phase 2 clinical trials. Surrogate efficacy models are validated.	Clinical trials are conducted to demonstrate safety of candidate Class III medical device in a small number of humans under carefully controlled and intensely monitored clinical conditions. Component tests, component drawings, design history file, design review, and any DMR are updated and verified. Production technology demonstrated through production-scale cGMP plant qualification. For 510(k), component tests, component drawings, design history file, design review, and any DMR are updated and verified. Manufacturing facility is ready for cGMP inspection.	Advanced technical testing of prototype HW/SW system, to include interfaces to actual supporting systems, is conducted in a relevant or simulated operational environment. Out-product is final prototype.
	TRL 6 Decision Criterion: Data from Phase 1 trials meet clinical safety requirements and support proceeding to Phase 2 clinical studies.	**TRL 6 Decision Criterion:** Data from Phase 1 clinical trials meet clinical safety requirements and support proceeding to Phase 2 clinical trials.	**TRL 6 Decision Criterion:** Data from the initial clinical investigation demonstrate that the Class III device meets safety requirements and support proceeding to clinical safety and effectiveness trials. For a 510(k), information and data demonstrate substantial equivalency to predicate device and support production of the final prototype and final testing in a military operational environment.	**TRL 6 Decision Criterion:** Medical Informatics data and knowledge management systems are tested with target applications in a laboratory environment. Configuration management approach developed.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	For Phase 1 Clinical Trials to begin, the following are needed: the FDA's and sponsor's summary minutes of pre-IND meeting document agreements and general adequacy of information and data to support submission of IND application. Review of the submitted IND application does not result in a FDA decision to put a clinical hold on Phase 1 clinical trials with the candidate drug. For entry into Phase 2 clinical trials, the results from Phase 1 clinical studies have to demonstrate safety of candidate drug. An updated IND application, amended with a new clinical protocol to support Phase 2 clinical trials or a surrogate test plan and submitted to the FDA, documents the achievement of this criterion.	For Phase 1 Clinical Trials to begin, the following are needed: the FDA's and sponsor's summary minutes of pre-IND meeting document agreements and general adequacy of information and data to support submission of an IND application. Review of the submitted IND does not result in an FDA decision to put a clinical hold on Phase 1 clinical trials with the candidate biologic/vaccine. For entry into Phase 2 clinical trials, the results from Phase 1 clinical studies have to demonstrate safety of candidate biologic/vaccine. An updated IND, amended with a new clinical protocol to support Phase 2 clinical trials or surrogate test plan and submitted to the FDA, documents achieving this criterion.	Documentation from clinical study results shows the candidate device is safe. Changes to the investigational plan that require FDA approval (21CFR812.35) are submitted as a supplemental IDE application to the FDA. For a 510(k), reviewers confirm adequacy of documented component tests, component drawings, design history file, design review, and any DMR to support claim of substantial equivalency and readiness for final testing in a military operational environment.	

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 7 **NASA/*Defense Acquisition Guidebook* TRL Definition:** System prototype demonstration in an operational environment				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)[N1, N2]**	**Medical Devices[N3, N4]**	**Medical IM/IT & Medical Informatics**
Prototype near, or at, planned operational system. Represents a major step up from TRL 6, requiring demonstration of an actual system prototype in an operational environment (e.g., in an aircraft, in a vehicle, or in space). Examples include testing the prototype in a test-bed aircraft.	Phase 2 clinical trials are conducted to demonstrate initial efficacy and capture further safety and toxicity data. Product activity (e.g., preliminary evidence of efficacy) is determined. Product final dose, dose range, schedule, and route of administration are established from clinical pharmacokinetic and pharmacodynamic data. Phase 2 clinical trials are completed. Data are collected, presented, and discussed with CDER at pre-Phase 3 meeting (Type B) in support of continued drug development. Clinical endpoints and/or surrogate efficacy markers and test plans agreed to by CDER.	Phase 2 safety and immunogenicity trials are conducted. Product immunogenicity and biological activity (e.g., preliminary evidence of efficacy) are determined. Product final dose, dose range, schedule, and route of administration are established from vaccine immunogenicity and biologic activity and, when necessary, from clinical pharmacokinetics and pharmacodynamics data. Phase 2 clinical trials completed. Data are collected, presented, and discussed with CBER at pre-Phase 3 (or surrogate efficacy) meeting (Type B) in support of continued development of the biologics/vaccines. Clinical endpoints and/or surrogate efficacy markers and test plans agreed to by CBER.	Clinical safety and effectiveness trials are conducted with a fully integrated Class III medical device prototype in an operational environment. Continuation of closely controlled studies of effectiveness and determination of short-term adverse events and risks associated with the candidate product. Functional testing of candidate devices is completed and confirmed, resulting in final down-selection of prototype device. Clinical safety and effectiveness trials are completed. Final product design is validated, and final prototype and/or initial commercial scale device is produced. Data are collected, presented, and discussed with CDRH in support of continued device development. For a 510(k), final prototype and/or initial commercial-scale device are produced and tested in a military operational environment.	Prototype HW/SW system is near or at planned operational system. Actual system prototype is demonstrated in an operational environment with end-users (first cut user test).
	TRL 7 Decision Criterion: Phase 3 clinical study plan or surrogate test plan has been approved.	**TRL 7 Decision Criterion:** Phase 3 clinical study plan or surrogate test plan has been approved.	**TRL 7 Decision Criterion:** Clinical endpoints and test plans are agreed to by CDRH. For a 510(k), information and data demonstrate substantial equivalency to predicate device and use in a military operational environment and support preparation of 510(k).	**TRL 7 Decision Criterion:** Medical Informatics data and knowledge management systems are operationally integrated and tested with target applications in an operational environment.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	FDA's summary minutes of pre-Phase 3 meeting with sponsor discussing results of Phase 1 and Phase 2 trials and protocols or test plans provide a record of agreements and basis for sponsor to proceed with Phase 3 clinical study or surrogate test plan. An updated IND application, amended with a new clinical protocol to support Phase 3 clinical trials or surrogate test plan and submitted to the FDA, documents the achievement of this criterion.	FDA's summary minutes of pre-Phase 3 meeting with sponsor discussing results of Phase 1 and Phase 2 trials, as well as clinical protocols or test plans, provide record of agreements and basis for sponsor to proceed with Phase 3 clinical study or surrogate test plan. An updated IND application, amended with a new clinical protocol to support Phase 3 clinical trials or surrogate test plan and submitted to the FDA, documents achieving this criterion.	The FDA's and sponsor's summary minutes of their meeting documents any agreements reached regarding continued development of the Class III medical device. PMA shell modules (e.g., sections of PMA) are submitted to CDRH by sponsor if such submissions were previously approved by CDRH. For a 510(k), documented results of testing in an operational environment support safety, effectiveness, and use of device in a military operational environment.	

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 8 **NASA/*Defense Acquisition Guidebook* TRL Definition:** Actual system completed and qualified through test and demonstration				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)[N1, N2]**	**Medical Devices[N3, N4]**	**Medical IM/IT & Medical Informatics**
Technology has been proven to work in its final form and under expected conditions. In almost all cases, this TRL represents the end of true system development. Examples include developmental test and evaluation of the system in its intended weapon system to determine if it meets design specifications.	Implementation of expanded Phase 3 clinical trials or surrogate tests to gather information relative to the safety and effectiveness of the candidate drug. Trials are conducted to evaluate the overall risk-benefit of administering the candidate product and to provide an adequate basis for drug labeling. Process validation is completed and followed by lot consistency/ reproducibility studies. Pre-NDA (New Drug Application) meeting (Type B) held with CDER. NDA is prepared and submitted to CDER. Facility PAI is completed.	Implementation of expanded Phase 3 clinical trials or surrogate tests to gather information relative to the safety and effectiveness of the candidate biologic/vaccine. Trials are conducted to evaluate the overall risk-benefit of administering the candidate product and to provide an adequate basis for product labeling. Process validation is completed and followed by lot consistency/reproducibility studies. Pre-BLA (Biologics License Application) meeting (Type B) held with CBER. BLA is prepared and submitted to CBER. Facility PAI is completed.	Implementation of clinical trials to gather information relative to the safety and effectiveness of the device. Trials are conducted to evaluate the overall risk-benefit of using the device and to provide an adequate basis for product labeling. Confirmation of QSR compliance, the design history file, design review, and any DMR are completed and validated, and device production is followed through lot consistency and/or reproducibility studies. Pre-PMA meeting held with CDRH. PMA prepared and submitted to CDRH. Facility PAI (cGMP/QSR/ Quality System Inspection Technique (QSIT)) is completed. For 510(k), prepare and submit application.	Technical testing of final product. HW/SW system has been proven to work in its final form and under expected conditions.
	TRL 8 Decision Criterion: Approval of the NDA for drug by CDER.	**TRL 8 Decision Criterion:** Approval of the BLA for biologics/vaccines by CBER.	**TRL 8 Decision Criterion:** Approval of the PMA (or, as applicable, 510(k)) for device by CDRH.	**TRL 8 Decision Criterion:** Developmental test and evaluation of the HW/SW system in its intended environment demonstrate that it meets design specifications. Fully integrated and operational medical informatics data and knowledge management systems are validated in several operational environments.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	FDA issuance of an Approval Letter after their review of the NDA submitted by the sponsor for the drug documents this criterion.	FDA issuance of an Approval Letter after their review of the BLA application submitted by the sponsor for the pharmaceutical (biologic/vaccine) documents this criterion.	FDA issuance of an Approval Order after their review of PMA application submitted by the sponsor for the Class III medical device. The submitted PMA includes general information, summary of safety and effectiveness data, device description and manufacturing information, summaries of non-clinical and clinical studies, labeling, and instruction manual. For a 510(k), FDA issuance of a Marketing Clearance Letter (also referred to as a "substantially equivalent letter") after their review of 510(k) application submitted by the sponsor for the medical device.	

Table E-1. Proposed TRLs for Medical RDT&E (Continued)

TRL 9 NASA/*Defense Acquisition Guidebook* **TRL Definition:** Actual system proven through successful mission operations				
NASA/ *Defense Acquisition Guidebook* TRL Description	***USAMRMC Equivalent TRL Descriptions***			
	Pharmaceutical (Drugs)[N1, N2]	**Pharmaceutical (Biologics, Vaccines)[N1, N2]**	**Medical Devices[N3, N4]**	**Medical IM/IT & Medical Informatics**
Actual application of the technology in its final form and under mission conditions, such as those encountered in operational test and evaluation. Examples include using the system under operational mission conditions.	The pharmaceutical (i.e., drug) or medical device can be distributed/marketed. Post-marketing studies (non-clinical or clinical) may be required and are designed after agreement with the FDA. Post-marketing surveillance.	The pharmaceutical (i.e., biologic or vaccine) or medical device can be distributed/marketed. Post-marketing studies (non-clinical or clinical) may be required and are designed after agreement with the FDA. Post-marketing surveillance.	The medical device can be distributed/ marketed. Post-marketing studies (non-clinical or clinical) may be required and are designed after agreement with the FDA. Post-marketing surveillance.	Operational testing of the product. HW/SW system is in its final form and under mission conditions, such as those encountered in operational test and evaluation. Medical Informatics knowledge maintenance and verification of data integrity are ongoing. Military requirements met for transportation, handling, storage, and so forth.
	TRL 9 Decision Criterion: None. Continue surveillance.	**TRL 9 Decision Criterion:** None. Continue surveillance.	**TRL 9 Decision Criterion:** None. Continue surveillance.	**TRL 9 Decision Criterion:** Product successfully used during military mission as component of initial operational test and evaluation (IOT&E) phase. Logistical demonstration successfully conducted.
	Supporting Information	**Supporting Information**	**Supporting Information**	
	FDA transmits any requirement for post-marketing studies. Begin post-approval reporting requirements. Maintain cGMP compliance.	FDA transmits requirements for any post-marketing studies. Begin post-approval reporting requirements. Maintain cGMP compliance.	FDA transmits requirements for any post-marketing studies. Begin post-approval reporting requirements. Maintain cGMP compliance.	

Note 1 for Table E-1: *These guidelines are not considered absolutes, and characterization of activities associated with TRLs can and does vary at times. For example, experience to date in applying the guidelines for biomedical TRLs indicates considerable variation in the timing, activities, and programmatic events associated with TRLs 5 and 6 for pharmaceuticals. Hence, the S&T and acquisition PMs work together in exercising discretion in the selection, progression, and timing of specific activities to be accomplished in the attainment of TRL 5. Such flexibility and tailoring are needed to align the TRL decision criteria appropriately with the maturation and risk characteristics of a particular technology, including consideration of the associated investment strategy and transition procedures that may vary among PMs.*

Note 2 for Table E-1: *Descriptions and decision criteria are from Biomedical Technology Readiness Levels (TRLs), prepared for the Commander, U.S. Army Medical Research and Materiel Command under Contract DAMD17-98-D-0022, Science Applications International Corporation, 3 June 2003.*

Note 3 for Table E-1: *These guidelines are not considered absolutes, and characterization of activities associated with TRLs can and does vary at times. For example, experience to date with application of the guidelines for biomedical TRLs indicates considerable variation in the timing, activities, and programmatic events associated with medical devices that follow a 510(k) vis-à-vis the PMA path. Hence, the S&T and acquisition PMs work together in exercising discretion in the selection, progression, and timing of specific activities to be accomplished in the attainment of particular TRLs. Such flexibility and tailoring are needed to align the TRL decision criteria appropriately with the maturation and risk characteristics of a particular technology, including consideration of the associated investment strategy and transition procedures that may vary among PMs.*

Note 4 for Table E-1: *Descriptions and decision criteria are from Biomedical Technology Readiness Levels (TRLs), prepared for the Commander, U.S. Army Medical Research and Materiel Command under Contract DAMD17-98-D-0022, Science Applications International Corporation, 3 June 2003. Definitions pertain predominately to Class II and Class III devices (see 21CFR860.3 or Glossary of this appendix for device class definitions) that are subject to approval via the PMA process. Devices that are subject to approval via the 510(k) process (Market clearance; generally limited to certain Class I and Class II devices) may not require all of the studies described and only require an IDE if human studies are necessary.*

E.2 The FDA Regulatory Process

To protect U.S. public health, the FDA regulates products by ensuring that human pharmaceuticals (drugs and biologics/vaccines) are safe and effective and that reasonable assurance exists concerning the safety and effectiveness of medical devices intended for human use. Three FDA centers are charged with this mission:

1. **The Center for Drug Evaluation and Research (CDER).** CDER regulates drugs and some biologic products (antibodies, cytokines, growth factors, enzymes, and proteins extracted from animals or microorganisms).

2. **The Center for Biologics Evaluation and Research (CBER).** CBER regulates vaccines, blood and plasma products, viral-vectored gene therapy, products composed of human or animal cells, antitoxins, and select *in vitro* diagnostics. CBER also holds regulatory authority over Human Immunodeficiency Virus (HIV) test kits and medical devices involved in collecting, processing, testing, manufacturing, and administering blood products.

3. **The Center for Devices and Radiological Health (CDRH).** CDRH is responsible for regulating manufactured, repackaged, relabeled, and/or imported medical devices that are sold in the United States (except those devices regulated by CBER).

E.2.1 Pharmaceuticals

Drugs and biologics/vaccines follow parallel developmental regulatory pathways (see Table E-1). During preclinical development, the sponsor evaluates the toxicology and pharmacology of the new drug or biologic through *in vitro* and animal testing. Preclinical test results and any available past human experiences of the drug or biologic are incorporated in an IND application and submitted to the FDA for review. If no safety issues are found, human clinical testing of the new drug or biologic can be initiated after 30 days. Clinical testing proceeds in three successive phases, starting with a small group of human subjects (Phase 1) and progressing to a larger population of human subjects (Phase 3). Only qualified investigators, selected by the sponsor in accordance with Good Clinical Practice (GCP) (21CFR312.53 and 21CFR312.62), conduct clinical trials. The safety and effectiveness results of clinical testing comprise the most important factor in the approval or disapproval of the new drug or biologic. All active INDs require submission of an annual IND report to the FDA. The results of the human clinical tests and all chemistry and manufacturing information are submitted either in an NDA for drug products or a BLA for biologic products. The appropriate FDA center reviews the NDA or BLA, and, upon approval, the drug or biologic product can be entered into interstate commerce or marketed in the United States. FDA approval is for the specific indication(s) identified in the marketing application. Additional or modified medical indications require the submission of an amendment or a new marketing application. A new marketing application may require additional human clinical data acquired through IND

regulations. With some new drugs or biologics/vaccines, the FDA may require additional reporting requirements after approval, termed Phase 4 or post-marketing surveillance. Manufacturers are required to track and report the number and severity of adverse events attributable to each product for a specified time period. Severe adverse events detected during post-approval can lead to a product recall or mandatory withdrawal from the market. All drugs and biologics/vaccines must comply with cGMP and labeling regulations.

With certain drugs or biologic products, human clinical studies are not ethical or feasible because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers. In 2002, the FDA addressed this issue with new regulations that allow for the approval of new drug and biologic products based on evidence of effectiveness in animals (21CFR314 and 21CFR601). In February 2003, under the new federal regulations, DoD was able to gain approval of pyridostigmine bromide for prophylaxis against the lethal effects of the soman nerve agent.

E.2.2 Medical Devices

The FDA CDRH regulates most medical devices, and they have classified each device in the Code of Federal Regulations (CFR). Classification of devices into one of three classes is based on the level of regulatory control that is necessary to ensure the safety and effectiveness of a medical device, with Class I and Class III devices being the least and most regulated, respectively. The sponsor normally proposes the classification level of a device, using 21CFR860 as a guide. Most importantly, the classification of the device will identify, unless exempt (e.g., most of the Class I devices), the marketing process (either premarket notification (510(k)) or PMA (Premarket Approval)) that the manufacturer must complete to obtain FDA clearance/approval for marketing. All classified medical devices are subject to cGMP and labeling requirements. An approved 510(k) or PMA allows an applicant to market a particular device for its intended purpose.

The FDA approves most medical devices for marketing in the United States through a premarket notification (510(k)). The applicant must show that the new device is substantially equivalent to one or more predicate devices legally marketed in the United States. A description of all tests conducted and the results obtained must be provided in sufficient detail to allow the FDA to determine substantial equivalence. If the medical device is found to be substantially equivalent, the FDA will send the manufacturer a "substantially equivalent letter" to clear the device for marketing. If the FDA finds the device not to be substantially equivalent, the FDA sends the manufacturer a "not substantially equivalent letter," and the device cannot be marketed. At this point, the manufacturer can submit another 510(k) with new and/or additional information to support substantial equivalence or may be required to submit a PMA.

To allow a Class III medical device (devices that support or sustain human life or present a potential risk of serious illness or injury) into interstate commerce or marketing, a PMA is required. A PMA is the most stringent regulatory submission for medical devices. Class III devices follow somewhat different development and regulatory paths compared with those for

drugs and biologics/vaccines (see Table E-1). For example, if human clinical information is required to establish safety and efficacy, the regulatory application that allows human clinical trials is called an IDE. Approval of an IDE allows the initiation of human clinical trials of an investigational device. Qualified principal investigators (PIs), selected by the sponsor in accordance with 21CFR812.43, conduct clinical trials. All active IDEs require submission of an annual report to the FDA. Safety and efficacy information acquired during the IDE process is used to support the submission of a PMA, and the FDA must approve the PMA before the device can be marketed. As with drugs and biologics/vaccines, the FDA may mandate a period of post-marketing surveillance during which device-related adverse events must be tracked and reported.

E.3 Web Sites

FDA Center for Devices and Radiological Health (CDRH):
http://www.fda.gov/cdrh/

FDA Center for Drug Evaluation and Research (CDER):
http://www.fda.gov/cder/

FDA Center for Biologics Evaluation and Research (CBER):
http://www.fda.gov/cber/

E.4 Additional Information

Federal Food, Drug, and Cosmetic (FD&C) Act
United States Code, Title 21 – Food and Drugs (21 U.S.C.)
Chapter 9: Federal Food, Drug, and Cosmetic Act
http://www4.law.cornell.edu/uscode/uscode21/usc_sup_01_21_10_9.html

FDA Regulations
CFR: Title 21 – Food and Drugs (21CFR)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm or
http://www.gpoaccess.gov/cfr/index.html

Drug Approval
The CDER Handbook: http://www.fda.gov/cder/handbook/
CDERLearn: http://www.fda.gov/cder/learn/CDERLearn/default.htm

Medical Device Approval
Device Advice: http://www.fda.gov/cdrh/devadvice/index.html

Laws Enforced by the FDA
http://www.fda.gov/opacom/laws/

Protection of Human Subjects
32CFR219- *Protection of Human Subjects* (also referred to as the "Common Rule") (http://www.access.gpo.gov/nara/cfr/waisidx_02/32cfr219_02.html)

Department of Defense Directive (DoDD) 3216.2 (April 24, 2007) *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*
http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf

Glossary for Appendix E[5]

Approval Letter: A written communication to an applicant from the FDA approving an application or an abbreviated application to market a drug. [21CFR314.3]

Approval Order: A written communication to an applicant from the FDA approving a PMA for a Medical Devices application. [21CFR814.44]

Biologic or Biological Product: Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man. [21CFR600.3]

Biologics License Application (BLA): An application to the FDA for approval to market a biological product. [21CFR601.12]

current Good Manufacturing Practice (cGMP): Regulations that cover the methods used in and the facilities and controls used for the design, manufacture, packaging, storage, and installation of devices. [21CFR820]

Class (Device): One of the three categories of regulatory control for medical devices. [21CFR860.3]

Class I Device: The class of devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. In the absence of sufficient information to make that determination, the device is not life supporting and does not present a potential unreasonable risk of illness or injury. [21CFR860.3]

Class II Device: The class of devices for which general controls alone are insufficient to provide reasonable assurance of its safety and effectiveness and for which there is sufficient information to establish special controls, including the promulgation of performance standards. For a device that is purported to be for use in supporting human life, the Commissioner (FDA) shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness. [21CFR860.3]

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[5] Complete definitions and explanations of terms can be found in the source cited in brackets. CFR is an acronym for the Code of Federal Regulations (e.g., [21CFR3143.3]), U.S.C. is an acronym for United States Code (e.g., [21 U.S.C. 301-397], and FR is an acronym for the Federal Registry (e.g., [62 FR 25692]).

Class III Device: The class of devices for which premarket approval is or will be required. A device is in Class III if insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness, if the device is life supporting, or if the device presents a potential unreasonable risk of illness or injury. [21CFR860.3]

Classification Name: The term used by the FDA and its classification panels to describe a device or class of devices for purposes of classifying devices under section 513 of the Federal Food, Drug, and Cosmetic (FD&C) Act. [21CFR807.3]

Approximately 1,700 different generic types of devices are grouped into 17 medical specialties [21CFR862–895], as follows:

862: Clinical Chemistry and Clinical Toxicology Devices
864: Hematology and Pathology Devices
866: Immunology and Microbiology Devices
868: Anesthesiology Devices
870: Cardiovascular Devices
872: Dental Devices
874: Ear, Nose, and Throat Devices
876: Gastroenterology-Urology Devices
878: General and Plastic Surgery Devices
880: General Hospital and Personal Use Devices
882: Neurological Devices
884: Obstetrical and Gynecological Devices
886: Ophthalmic Devices
888: Orthopedic Devices
890: Physical Medicine Devices
892: Radiology Devices
895: Banned Devices.

Clinical Hold: An FDA order to delay proposed clinical investigation or to suspend an ongoing investigation. [21CFR312.42]

Clinical Investigation: Any experiment in which a drug that involves one or more human subjects is administered, dispensed, or used. For this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. [21CFR312.3]

Clinical Trial/Clinical Study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or identify any adverse reactions to an investigational product(s), and/or study absorption, distribution, metabolism, and excretion of an investigational product(s) with

the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. [62 FR 25692][6]

Cosmetic: (1) Articles intended to be rubbed, poured, sprinkled or sprayed on, or introduced into or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering appearance and (2) articles intended for use as a component of any such article. This term shall not include soap.

Device Master Record (DMR): A compilation of records containing the procedures and specifications for a finished device. [21CFR820.3]

Drug or Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body. [21CFR314.3]

Drug Product: A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. [21CFR314.3]

FD&C Act: The Federal Food, Drug, and Cosmetic Act. [21 U.S.C. 301-397]

FDA-Approved: An FDA designation given to drugs, biologics, and medical devices that have approved marketing applications. Additional or modified medical indications for use require the submission of an amendment or a new marketing application. A new marketing application may require additional human clinical data acquired through IND regulations.

General Controls: The baseline requirements of the FD&C Act that apply to all medical devices. In addition to prohibiting adulteration, misbranding, and banned devices, the general controls contain requirements for device manufacturers. These requirements include device listing, proper labeling, (manufacturing) establishment registration, and premarket notification (510(k)).

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. It provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected. [62 FR 25692]

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[6] 62 FR 25692 (May 9, 1997) is an International Conference on Harmonisation (ICH) document called *Good Clinical Practice: Consolidated Guideline*. This document addresses GCP principles that were adopted for use as guidance for industry. ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures that are required to ensure and assess the safety, quality and efficacy of medicines.

Good Laboratory Practice (GLP): Practices for conducting non-clinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA. [21CFR58.1]

Investigational Device Exemption (IDE): Allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a PMA application or a Premarket Notification (510(k)) submission to the FDA. [21CFR50, 56, 812]

Investigational New Drug (IND): A new drug or biologic that is used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes. [21CFR312.3]

IND Application: Allows a pharmaceutical (drug/biologic) to be used in a study under carefully controlled and intensely monitored conditions in order to collect safety and effectiveness data required to support an NDA or BLA. [21CFR312.3]

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (or PI). [62 FR 25692]

Label: Any display of written, printed, or graphic matter on the immediate container or package of, or affixed to any article.

Labeling: Any written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment in interstate commerce. This includes manuals, brochures, advertising, and so forth.

License: The terminology used for FDA's approval to market a biological pharmaceutical for a given set of indications (see also **FDA Approved**).

Life-Supporting or Life-Sustaining Device: A device that is essential to or that yields information that is essential to the restoration or continuation of a bodily function important to the continuation of human life. [21CFR860.3]

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory that is

- Recognized in the official National Formulary or U.S. Pharmacopoeia or any supplement to them
- Intended for use in diagnosing disease or other conditions or in curing, mitigating, treating, or preventing disease in man or other animals
- Intended to affect the structure or any function of the body of man or other animals and does not achieve any of its primary intended purposes through chemical action

within or on the body of man or other animals and is not dependent upon being metabolized for achievement of any of its primary intended purposes (Section 201(h) of the FD&C Act)).

New Drug Application (NDA): An application to the FDA for approval to market a new drug. [21CFR314.50]

Preapproval Inspection (PAI): An FDA inspection of a facility to

- Verify the integrity (truthfulness, accuracy, and completeness) of data submitted in support of an application
- Evaluate the manufacturing controls for the preapproval batches upon which the application is based to be certain that the company can actually meet the commitments in the chemistry, manufacturing, and controls (CMC) section of the application
- Evaluate the capability of the manufacturer to comply with GMPs
- Collect samples for analysis.

Post-marketing Surveillance: Tracking and reporting the number and severity of adverse events attributable to each product. This may be a requirement for licensure for a defined period of time following licensure.

Premarket Approval (PMA) for Medical Devices: Because of the level of risk associated with Class III devices, an applicant must receive FDA approval of its PMA application before marketing the device. PMA approval is based on the FDA's determination that the PMA contains sufficient valid scientific evidence to ensure that the device is safe and effective for its intended use(s). [21CFR814]

Premarket Notification (510(k)): An application submitted to the FDA to demonstrate that a device is substantially equivalent (see 21 U.S.C. 513(I)(1)(A)) to a device that is legally in commercial distribution in the United States before May 28, 1976, or to a device that has been determined by FDA to be substantially equivalent. [21CFR807.81]

Quality System Inspection Technique (QSIT): An FDA inspection technique that focuses on the first four elements of the seven inspectional subsets of the Quality System Regulation (QSR).

Quality System Regulation (QSR): The 1996 rewrite of the device section of the cGMPs. [21CFR820]

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (ADR): Any untoward medical occurrence that at any dose

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Causes a congenital anomaly/birth defect.

Special Controls: Class II devices include any device for which reasonable assurance of safety and effectiveness can be obtained by applying "special controls." Special controls can include special labeling requirements, mandatory performance standards, patient registries, and post-market surveillance.

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. [62 FR 25692]

Subject: A human who participates in an investigation, either as a recipient of the IND or as a control. [21CFR312.3]

Substantial Equivalence (SE): A device is substantially equivalent if, in comparison to a legally marketed device, it has the same intended use as a predicate device and has the same technological characteristics as the predicate device. SE does not mean the devices are identical. [21CFR807.87]

Type B Meeting: Type B meetings are as follows: (1) pre-IND meetings (21CFR312.82), (2) certain end of Phase 1 meetings (21CFR312.82), (3) end of Phase 2/pre-Phase 3 meetings (21CFR312.47), and (4) pre-NDA/BLA meetings (21CFR312.47)

Attachment 1C: Technology Readiness Levels for Medical Countermeasure Products (Drugs and Biologics)

For Areas of Interest 4 and 5, Offerors must identify in their Quad Chart and White Paper that the criteria for TRL 6 have been met for the proposed product and for the proposed influenza indication, using the *Technology Readiness Levels for Medical Countermeasure Products (Drugs and Biologics)* as shown below. Please note that all activities within a TRL level (or sublevel) must be completed to have achieved that TRL status. These TRL criteria can also be found at:

http://www.medicalcountermeasures.gov

FOR USE WITH AREAS OF INTEREST 4 AND 5

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).*

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)).

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.

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)**[1] Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate.[4] Conduct Phase 2 clinical trial(s).[3] **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.2 **7B** Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2).[3]

1 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

2 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.

TRL 8	**Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials3, 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.[3] **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.3 **9B** Maintain manufacturing capability as appropriate.

3 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: Breakdown Of Proposed Estimated Cost (Plus Fee) And Labor Hours

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 business proposal. For security purposes, please include a hard copy of the completed spreadsheet and submit the electronic file on a diskette with your proposal.

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 3: Security Template

Section I. <u>Security Administration:</u>

1. Security Program: If requested, the Offeror's security template shall include a comprehensive security program that provides a security plan for the overall protection of personnel, information, data, and facilities associated with fulfilling the BARDA requirement. The Offeror's proposal shall include a security plan which establishes security practices and procedures that demonstrate how the Offeror will meet and adhere to the security requirements outlined in Section II (noted below) by time of contract award. The Offeror shall also ensure that other entities (sub-contractors, consultants, etc.) performing work on behalf of the Offeror establishes and manages a security program that is in compliance with BARDA security requirements.

2. Facility Security Plan: The Offeror's security plan will include the following processes and procedures at a minimum:

(a) Security Administration: Organization and responsibilities; security risk assessment for site; threat levels identification; security procedures during elevated threats; liaison with law enforcement; security education and training.

(b) Personnel Security Policies and Procedures*:* Candidate recruitment process; background investigations; employment suitability policy; access determination; rules of behavior/ conduct; termination procedures; non-disclosure agreements.

(c) Physical Security Policies and Procedures: Internal / external access control; protective services; identification/ badging; visitor access controls; parking areas and access control; perimeter fencing / barriers; shipping, receiving and transport; security lighting; restricted areas; signage; intrusion detection systems; alarm monitoring / response; closed circuit television; product storage security; other control measures.

(d) Information Security: Identification of sensitive information; access control; storage of information; document control; retention/ destruction requirements.

(e) Information Technology Security Policies and Procedures: Intrusion detection and prevention systems; employee training; encryption systems; identification of sensitive information/ media; password policy; removable media policy; laptop policy; media access control/ determination; secure storage; system document control; system backup; system disaster recovery.

3. Site master plan: Offeror shall provide a site schematic for security systems which includes: main access points; security cameras; electronic access points; bio-containment laboratories.

4. Site threat / risk assessment: Offeror shall provide a written risk assessment for the facility addressing: criminal threat; terrorist threat; industrial espionage; natural disasters; and potential loss of critical infrastructure (power/water/natural gas, etc.) This assessment shall include recent data obtained from local law enforcement agencies.

Section II. <u>Security Requirements:</u>

1. Physical Security:

(a) **Closed Circuit Television (CCTV) Monitoring:**

- CCTV with time lapse video recording for exits / entrances to the facility and buildings where critical assets are processed and stored.
- Video recordings maintained for a minimum of 30 days.

(b) **Lighting**:

- Lighting covering perimeter, parking areas, entrances/exits. Lighting should have emergency power backup and be sufficient for CCTV.

(c) **Receiving and Shipping:**

- Receiving and shipping areas must have controlled access and contingency plans that implement modified procedures to restrict shipping and receiving to mission critical products during times of elevated threat.

(d) **Physical Access Control:**

- Intrusion Detection System with centralized monitoring system capability.
- Immediate notification / response to any alarms.
- Electronic system (i.e. card key) utilized to control access to areas where assets critical to the contract are located (facilities, laboratories, clean rooms, production facilities, warehouses, etc.)

(e) **Employee/Visitor Identification:**

- Photo identification for all personnel displayed at all times.
- Visitor control; identification; screening and accountability system.

(f) **Security Fencing:**

- Requirements for security fencing will be determined by the criticality of the program and the potential threat environment.

(g) **Protective Security Forces:**

- Requirements for a security force at the facility will be determined by the criticality of the program and the potential threat environment.

2. Security Operations:

(a) **Information Sharing:**

- Establish liaison with law enforcement and procedures for receiving and disseminating threat information.

(b) **Training:**

- Conduct new employee security awareness training.
- Conduct and maintain records of annual security awareness training.

(b) **Security Management:**

- Designate a knowledgeable employee to manage security operations.

3. Personnel Security:

(a) **Records Checks / Interview:**

- Verification of date of birth; citizenship; education; previous employment (5 year history); previous residences (5 year history); national / local criminal records search; and a personal interview of candidate.

(b) **Hiring / Retention Standards:**

- Policies concerning hiring and retention of employees to include employee conduct and behavior standards.

4. Information Security:

(a) **Physical Document Control:**

- Applicable documents shall be identified and marked as procurement sensitive, proprietary or with appropriate Government markings.
- Sensitive, proprietary and Government documents should be maintained in a lockable filing cabinet / desk or other storage device.

(b) **Document Destruction**

- Documents shall be destroyed using approved destruction measures (i.e. shredders / third party vendor / pulverizing / incinerator).

5. Information Technology Security:

(a) **Access:**

- Limit information system access to authorized users.
- Identify information system users, processes acting on behalf of users, or devices and authenticate identities before allowing access.
- Limit physical access to information systems and equipment.

(b) **Training:**

- Ensure that personnel are trained and are made aware of the security risks associated with their activities and of the applicable laws, policies, standards, regulations, or procedures related to IT systems.

(c) **Audit and Accountability:**

- Create, protect, and retain information system audit records to the extent needed to enable the monitoring, analysis, investigation, and reporting of unlawful, unauthorized, or inappropriate information system activity; and ensure that the actions of individual information system users can be uniquely traced to those users.

(d) **Configuration Management:**

- Establish and enforce security configuration settings.

(e) **Contingency Planning:**

- Establish, maintain, and implement plans for emergency response, backup operations, and post-disaster recovery for information systems to ensure the availability of critical information resources.

(f) **Incident Response:**

- Establish an operational incident handling capability for information systems that includes adequate preparation, detection, analysis, containment, and recovery.

(g) **Media Protection:**

- Protect information system media, both paper and digital; limit access to information on information system media to authorized users; and sanitize or destroy information system media no longer needed.

(h) **Physical / Environmental Protection:**

- Limit physical access to information systems, equipment, and the respective operating environments to authorized individuals; protect the physical and support infrastructure for information systems;
- Protect information systems against environmental hazards; provide appropriate environmental controls in facilities containing information systems.

6. Transportation Security: Adequate security controls shall be implemented to protect materials while in transit from theft, destruction, manipulation, or damage. These security measures will be addressed in the Facility Security Plan.

7. Security Reporting Requirements: The Offeror shall immediately report to the Government any activity or incident that is in violation of established security standards or indicates the loss or theft of Government products. The facts and circumstances associated with these incidents will be documented in writing for Government review.

8. Security Audits: The Offeror agrees to formal security audits conducted at the discretion of the Government. Security audits may include both prime and sub locations.

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.

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: Government Notice for Handling Proposals

NOTE: This Notice is for the Technical Evaluation Panels that will be reviewing Full 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.

(f) 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.

(g) 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 6: Quad Chart Template

A quad chart that contains the following information must be included in Volume III, Supplemental Information, of the Full Proposal and must 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 Topic.

TITLE OF PROJECT, RESEARCH AREA ADDRESSED, PROGRAM DIRECTOR/MANAGER, COMPANY NAME
CONTACT INFORMATION (E-MAIL ADDRESS, PHONE NUMBER)

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 5 years total)

For more detailed information see Part IV.

Attachment 7: 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)

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 form in metric system and a description of identifying characteristics of dosage forms	*Summary information regarding completed or planned studies to support the 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.* *Include the studies in the development program that will address adverse reactions associated with a particular drug class.*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date*
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/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. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Attachment 8: Regulatory Guidance for Devices

Overview of Device Regulations
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm

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.

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.

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.

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 commercially 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

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.

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 Notification 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.

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:

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.

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.

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.

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 non-significant risk must be approved by the IRB only before the study can begin.

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.

The quality system regulation includes design controls (21 CFR 820.30) which must comply with during the design and development of the device.
Labeling - 21 CFR Part 801
Labeling includes labels on the device as well as descriptive and informational literature that accompanies the device.

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.

Attachment 9: Pre Proposal Conference

BARDA Multi-Broad Agency Announcement Pre-Proposal Conference 2013

Note: Offerors are encouraged to attend the conference. However, the conference will have limited seating.

The conference will take place with three sessions for all research areas of interest. We anticipate that each session will include a 30 minute BARDA presentation followed by 10 minute prescheduled individual meetings between BARDA and attendees. Each session shall last approximately one hour and thirty minutes. Sessions will occur simultaneously over the three hour period and you will receive a registration confirmation from BARDA informing you of which session you are scheduled to attend and with which BARDA area of interest you will have an individual meeting.

Date and Time	September 4, 2013 9:00AM – 12:00PM EDT
Location:	200 Independence Avenue S.W. Hubert H. Humphrey Building, Great Hall Washington, DC 20201

REGISTRATION

1. To register for the conference, visit the link http://www.phe.gov/about/amcg/baaconference-2013/Pages/default.aspx. Registration will close on **August 21, 2013** or when the event reaches capacity. Space is limited, so register today!

2. Attendance is limited to two (2) representatives per organization. Each organization is limited to a single meeting with BARDA program staff based on area of interest.

3. Each organization may register for a primary and secondary area of interest, and BARDA shall attempt to accommodate your selections in that order. We will assign you a 10 minute meeting with Program staff. Every effort will be made to accommodate everyone's first choice; depending upon the number of registrants. Meeting assignments will be provided upon arrival at the conference. If, after registering, you find that you must cancel, please let us know so that we can open up your meeting slot to other attendees.

Please note the following regarding the pre-proposal conference:

- Arrive 30 minutes early to allow time to clear security.
- Bring your identification (photo identification).
- The closest metro stop is Federal Center SW, serviced by the Blue and Orange Metrorail lines. At the top of the escalator turn left. The Humphrey Building is two blocks ahead on the right at the corner of 3rd St., SW and Independence Avenue, SW.
- Enter the Humphrey Building at the Independence Avenue Street entrance and register with the guard at the front desk to receive a visitor pass.

- Tape recorders and videos are prohibited.
- Presentation material from the conference will be posted on FedBizOpps in an amendment to the BAA following the pre-proposal conference.

*** Be advised that in order to obtain security clearance, advanced notification must be provided by all attendees who are not United States citizens. This includes residents holding Green Cards. Notification must be received no later than August 14, 2013. You will be advised what information we need (passport, visa information, etc.) when you register.**