DEFENSE THREAT REDUCTION AGENCY

CHEMICAL AND BIOLOGICAL DEFENSE PROGRAM

CHEMICAL / BIOLOGICAL TECHNOLOGIES DEPARTMENT

JSTO-CBD FY14/16 Service Call

SERVICE CALL FOR PROPOSALS

JOINT SCIENCE AND TECHNOLOGY OFFICE FOR CHEMICAL AND BIOLOGICAL DEFENSE
FY14/16

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1.0. INTRODUCTION AND SCOPE

1.1. Introduction.

1.1.1. The Defense Threat Reduction Agency's (DTRA) mission is to safeguard America and its allies from Weapons of Mass Destruction (WMD) (chemical, biological, radiological, nuclear, and high yield explosives) by providing capabilities to reduce, eliminate, and counter the threat, and mitigate its effects.

1.1.2. The Joint Chemical and Biological Defense Program (CBDP) was established by the Department of Defense (DoD) to provide state-of-the-art defense capabilities to allow military forces of the United States to operate and to successfully complete their missions in chemical and biological warfare environments. The scope of mission efforts and the priorities assigned to specific projects are influenced by changes in military and civilian Chemical and Biological Defense (CBD) science and technology, advanced developments, operational requirements, military threat assessments, and national defense strategies. To keep pace with defense capability requirements, the CBDP as part of its mission, routinely solicits chemical and biological research. The comprehensive research program encompasses both intramural and extramural sources, and the role of each is vital to the fulfillment of the Program objectives.

1.2. Scope*:*

1.2.1. This solicitation is an intramural Service Call focused on research ranging from basic research (6.1 funding), to more mature applied research (6.2 funding), advanced technology development (6.3 funding), and advanced component development and prototype (6.4 funding) during its multiple year term (FY 2014 – FY 2016). Proposals will be accepted and considered that combine Basic Research with Applied Research, Applied Research, and/or Advanced Technology Development as specified in each topic. For definitions of each type of research, see Appendix I.

1.2.2. The Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD) seeks high quality, innovative and relevant concepts to be considered for funding as new start initiatives.

Note: A parallel solicitation (Broad Agency Announcement (BAA)) for proposals for new initiatives from industry (to include small businesses) and academia is also being issued by JSTO-CBD, through www.fedbizopps.gov under the BAA number HDTRA1-14-CHEM-BIO-BAA. This Service Call is not a portal for receiving intramural research proposals that are collaborations with extramural proposals submitted in response to HDTRA1-14-CHEM-BIO-BAA.

2.0. PURPOSE

2.1. The purpose of this Service Call is to solicit research proposals for the CBDP.

2.2. The Chemical / Biological Technologies Department, in its continuing mission, is seeking new and innovative ideas for experimental and theoretical development of technologies to fill DoD requirements for chemical and biological defense. The goal is to identify and select science and technology projects that can be transitioned to joint acquisition programs. Proposals may only address the current topics presented in Appendices A-E of this document.

2.2.1. Proposals that address technologies at a Technology Readiness Level of 4 (TRL4) or greater should also be aware of the Manufacturing Readiness Level (MRL) considerations, where applicable.

2.3. The DOD CBDP, DTRA, and JSTO-CBD are seeking optimum approaches to meet technology objectives within the following areas: Diagnostics, Detection, and Disease Surveillance; Physical Science and Technology; Translational Medical; Advanced and Emerging Threats; and Information Systems Capability. General goals of each area are listed below.

2.3.1. Detection – Chemical and Biological: The goal of the Detection area is to provide real-time capability to detect, identify, characterize, locate and warn against all known or validated CB warfare agents in addition to other chemical or biological threat materials (e.g., Toxic Industrial Chemicals).

2.3.2. Information Systems Capability Development: The goal of the Information Systems Capability Development area is to provide information technology superiority with respect to the Chemical, Biological, Radiological, and Nuclear (CBRN) environment.

2.3.3. Protection – Individual and Collective: The Protection Capability Area seeks to provide unencumbered full-dimensional protection to the war fighter for both personal protective gear (individual protection) and protection of large scale fixed or mobile environments (collective protection).

2.3.4. Hazard Mitigation: The goal of the Hazard Mitigation Capability Area is to develop technologies that can rapidly restore pre-contamination capabilities with a minimum of logistical impact.

2.3.5. Threat Agent Science: The Threat Agent Science Capability Area seeks to maintain and develop scientific knowledge of current, non-traditional, and emerging threats in addition to studying areas such as low level toxicity, agent fate, and improved simulant materials.

2.3.6. Medical Pretreatments: The goal of the Pretreatments Capability Area is to conduct research in order to develop lead candidate vaccines and chemical pretreatments and protectants that can be administered before exposure to provide both specific and broad-spectrum protection against validated chemical or biological agents. Categories of threat agents addressed in this capability area include nerve agents, viruses, bacteria and toxins.

2.3.7. Medical Diagnostics: Medical diagnostics involves the diagnosis of infection by or exposure to bacterial, viral, or toxin agents (biological diagnostics) or of exposure to nerve, vesicant, respiratory and blood agents (chemical diagnostics) with the goal to rapidly identify the causative agent in a remote environment prior to onset of symptoms.

2.3.8. Medical Therapeutics: The goal of the Therapeutics Capability Area is to develop lead candidate medical treatments and pharmaceuticals that, when administered after exposure to a chemical or biological agent, mitigate or curtail the effects of that exposure and sustain forces operating in a CBW hazard area. Medical Therapeutics is segregated into biological countermeasures and chemical countermeasures.

2.3.9. Threat Surveillance - Chemical and Biological: The goal of the Threat Surveillance area is to deliver cutting edge Integrated Early Warning, Information Management and Applied Analytic capabilities to the warfighter; virtually connect them to these capabilities and other system users for rapid situational awareness, course of action (CoA) analysis and decision support.

3.0. ELIGIBILITY

All Federal agencies and organizations, Federal laboratories, Federally Funded Research and Development Centers (FFRDC) and Academic Institutions that are Federal government organizations are eligible to submit proposals in response to this intramural Service Call.

4.0. PROPOSAL SUBMISSION

4.1. Submission Overview. Submissions will be conducted in two phases. Phase I is for submission of Quad Charts/White Papers. The second submission, Phase II, is by invitation only and is based on the evaluation results of Phase I. The invitation to submit a Phase II proposal (i.e. full proposal submission consisting of Volume I - Technical Proposal, Volume II - Cost Proposal and Volume III - Supplemental Information, to include, but not limited to, a Statement of Work and an updated Quad Chart/White Paper) will be based on the evaluation results in Phase I.

4.2. General Application and Submission Information.

4.2.1. **Registration.** Registration at the DTRA proposal submission website, https://www.dtrasubmission.net is required of all Offerors who have not previously done so prior to submission of Phase I proposals. Prior registration at a proposal submission website other than the one identified above does not fulfill registration requirements for participation in this Service Call. Failure to register as stated will prevent submission of the required documents. The submission deadline is listed in the Milestone Schedule, Section 7.0.

4.2.2. Proposals must be submitted electronically through the DTRA proposal submission website, https://www.dtrasubmission.net. Proposals submitted by any means other than the DTRA proposal submission website (e.g., hand-carried, postal service mail, commercial carrier, or e-mail) will not be considered. Detailed registration and submission instructions are available at the website. All documents submitted to the DTRA proposal submission website are considered works in progress and are not eligible for evaluation until the Offeror submits the final proposal package for consideration. The final submission must be 'locked' on the DTRA proposal submission website; until a submission has been 'locked' (saved as final); the submission is not eligible for review. Look for this 'lock' icon  on the DTRA proposal submission website. Offerors are responsible for ensuring compliant and final locked submission of their proposals, and can verify the submission of the proposal package with the electronic receipt that appears on the screen following submission of a proposal to the DTRA proposal submission website.

All documents with the exception of the Phase I Quad Chart (see 4.3.2 below) must be submitted in a Portable Document File (PDF) format compatible with Adobe Acrobat ® version 11.0 or earlier. Movie and sound file attachments or other additional files will not be accepted. Perform a virus check before uploading proposal files. If a virus is detected, it may cause rejection of the file. Uploaded files must not be password protected or encrypted.

Offerors are responsible for ensuring compliant and final submission of their proposals, and can verify the submission of the proposal package with the electronic receipt that appears on the screen following compliant submission of a proposal to the DTRA proposal submission website.

4.2.3. <u>Classified Material:</u> CLASSIFIED PROPOSALS WILL NOT BE ACCEPTED UNDER THIS SERVICE CALL.

4.2.4. Cover Sheet Information: The following information is required to complete a Cover Sheet for each proposal:

- Topic Number proposal under which proposal is being submitted for consideration
- Title of proposed effort
- Applicant Institution name and address (this is based on the registrant submitting the proposal, and should be the laboratory, not the individual)
- Technology Focus (brief description)
- Estimated Cost per year of performance, and months of performance in each year
- Information on other submissions of same proposed effort
- Contact Information for PI and Business POCs – Name, Title, Phone, Fax and Email
- Identification of proprietary information included in proposal submission (page numbers)
- Technical Abstract (limited to 200 words with no classified or proprietary information)
- Key Words/Phrases (limited to 8 key words)

Once the cover sheet is saved, the system will assign a unique proposal number for each Phase I submission. Cover sheets may be edited as often as necessary until the submission period closes. All submission documents must be dated. If multiple proposals are being submitted by the same Offeror, separate cover sheets must be generated for each proposal and the Quad Chart and White Paper uploaded with the associated cover sheet

4.3. Phase I Pre-proposal.

4.3.1. Only one topic may be addressed in a Phase I Pre-proposal. Each Phase I file must not exceed 2 Megabytes of storage space (uncompressed). Phase I submissions will be evaluated using the criteria set forth in Section 4.3.4. Organizations whose proposals are selected will be invited to submit full proposals for evaluation under Phase II.

The Quad Chart and White Paper must be uploaded as two separate documents (two individual and separate files).

4.3.2. <u>Quad Chart Format</u>: All Quad Charts must include the information indicated below.

a. Heading: Title, Research Area Addressed, Topic Number, Title, Principal Investigator, Organization
b. Upper Left: Objective, Description of Effort
c. Lower Left: Benefits of Proposed Technology, Challenges, Maturity of Technology (Maturity information should indicate, where possible, the current TRL of proposed technology and anticipated level of the proposed technology at project completion); refer to Appendix F for established TRL categories.
d. Upper Right: Picture or graphic illustrating proposed technology development.
e. Lower Right: Milestones, Cost, Period of Performance, Contact Information.
f. Must be prepared/submitted in landscape format.

4.3.3. White Paper Narrative Format: The White Paper narrative expands on the Quad Chart presentation, and must not exceed four pages, 8.5 x 11 inches, single spaced, with one-inch margins in type not smaller than 12 point Times New Roman font, in portrait layout. The content of the White Paper narrative must be limited only to a further explanation of the information conveyed in the Quad Chart and shall include sufficient design elements to provide statistically defensible data. For example, a brief synopsis of planned major milestones and personnel is appropriate. Whenever possible, preliminary data collected in the investigator's laboratory, or available in the published literature, will be used to support and justify the research strategy. Offerors should further address prior work in the proposed area of study, listing project numbers if the proposed effort is a continuation of work already conducted or underway. DO NOT include corporate or personnel qualifications, past experience, or any supplemental information that is not requested of the Phase I Pre-proposal submission. Please also include brief information outlining any proposed human or animal subject testing, or verify that none is proposed. White papers should also briefly outline any collaboration planned for the proposed effort.

4.3.4. Evaluation Criteria: All information and documentation required and necessary for Phase I Pre-proposal evaluation must be contained in the submission. Proposals are encouraged that show a comprehensive approach with citation of supporting fundamental bases (theoretical or experimental data, preference is experimental data) and featuring teaming arrangements with other Service laboratories, Other Government Agencies (OGA), or other organizations that lend unique expertise or specialized facilities to the proposed effort. Phase I Pre-proposal submissions are evaluated based on the programmatic relevance and scientific merit of the submission as it relates to CBDP goals.

4.3.4.1. Scientific and Technical Merit: The objective of this criterion is to assess the extent to which the Offeror has an innovative, unique, high payoff, and comprehensive technical approach based on sound scientific principles. Offerors must demonstrate that their approach is innovative and unique, that the technical approach is sound, that they have an understanding of critical technical issues and risk and that they have a plan for mitigation of those risks. Significant improvements in chemical and biological technology capability above the 'state-of-the-art' are sought.

4.3.4.2. Value to the Joint Chemical and Biological Defense Program Goals: The objective of this criterion is to assess the extent to which the Offeror proposes to answer a basic knowledge question or address an applied/advanced research effort essential to a technology development of interest to the CBDP, and the value of the project deliverable (product, process, answer to basic science question) to the DoD and the general field of research. Offerors must demonstrate a clear knowledge of desired military capabilities and indicate the manner in which the technology will transition. Proposals must demonstrate how the proposed research supports the program goals and responds to the specific topic areas. Offerors must demonstrate that the new technology can be implemented or utilized by end-users as a means to improve their operational capabilities. Possible duplication with other research currently funded by the DoD or OGA is also considered.

4.3.5. Evaluation Results: A brief summary of the Government's evaluation will be made available to Offerors via the DTRA proposal submission website https://www.dtrasubmission.net upon finalization of the Phase I evaluations.

4.4. Phase II Proposal (By Invitation Only).

4.4.1. Notification to Offerors: Notifications of invitation to participate in Phase II and notifications of non-selection will be sent via e-mail to Offerors (specifically, the registered Business Point of Contact and the designated Principal Investigator as entered on the proposal cover page on the DTRA proposal submission website). The e-mail will be sent from the DTRA proposal submission website on or about the date specified in Section 7.0. A brief synopsis of the Government's evaluation in the form of a summary statement will be electronically available to Offerors via the DTRA proposal submission website. The e-mail notifications will advise of the statement availability.

4.4.2. Offerors must be aware that it is their responsibility to ensure that e-mail notifications reach the designated Business Point of Contact and Principal Investigator and that e-mail notifications are not blocked due to the use of 'spam blocker' software or other means. Additionally, it is the responsibility of the Business Point of Contact to inform DTRA of any updates to e-mail addresses for both themselves as the registered Business Point of Contact and for the designated Principal Investigator.

4.4.3. Technical Proposal: The Technical Proposal must not exceed 25 pages. If the proposal exceeds 25 pages, only the first 25 pages will be reviewed. A page is defined as 8 ½ x 11 inches, single-spaced, with one-inch margins in type not smaller than 12 point Times New Roman font. The technical proposal must be uploaded as a separate Portable Document File (PDF) compatible with Adobe Acrobat ® version 11.0 or earlier, and will not exceed 10 Mbytes of storage space.

The Technical Proposal should address the following:

- Objectives and relevance of the proposed research
- Background relating to the proposed research
- Experimental design and plans
- Technical risk and mitigation plans
- Major milestones for effort
- Discussion of available facilities
- Discussion of proposed personnel
- References

4.4.4. Cost Proposal: The cost proposal must include cost estimates sufficiently detailed for meaningful evaluation versions (see the tables below for an example of a detailed cost breakout) of the cost proposal.

4.4.4.1. PROPOSAL ADEQUACY The responsibility for providing adequate supporting data and attachments lies solely with the Offeror. Further, the Offeror must also bear the burden of proof in establishing reasonableness of proposed costs; therefore, it is in the Offeror's best interest to submit a fully supportable and well-prepared cost proposal. The basis and rationale for all proposed costs should be provided as part of the proposal so that Government personnel can place reliance on the information as current, complete, and accurate.

4.4.4.2. COST BREAKDOWN (developed in Microsoft Excel Format). Offeror format acceptable provided it includes a detailed cost breakdown of all costs by cost element in accordance with Tables 1 - 6: Sample Formats below. The Offeror must also provide a narrative to support the requirements in each cost element. In addition, the Offeror must provide a separate cost proposal, in the same level of detail as the

prime contractor for each subcontractor or consultant which were not selected on adequate price competition.

Cost elements should include the following:

a. LABOR: Individual labor categories or persons (principal investigator, graduate students, etc.), with associated labor hours and unburdened labor rates.
b. MATERIALS: Cost of materials, broken out to the level of detail shown in Table 2. Clearly delineate any computer or IT purchases.
c. EQUIPMENT: Cost of equipment, broken out to the level of detail shown in Table 3.
d. TRAVEL: Cost of each trip, broken out to the level of detail shown in Table 4.
e. OTHER DIRECT COSTS (ODC): Cost of ODCs, broken out to the level of detail shown in Table 5. Examples of ODCs include but are not limited to the following:
    i. Publication and report cost
    ii. Laboratory and Computer Usage Fees
    iii. Communication costs not included in overhead
f. SUBCONTRACTOR: Total cost for each subcontractor and/or consultant, broken out to the level of detail shown in Table 6. Any subcontractor not selected on the basis of adequate price competition must provide a separate cost break out that is in compliance with the requirements included in this Attachment.
g. INDIRECT COSTS.
    i. Fringe Benefits
    ii. Overhead
    iii. Material Handling
    iv. General and Administrative
h. FEE, if any.

4.4.4.3. COST NARRATIVE All Offerors are required to provide a narrative to support each cost element proposed.

a. LABOR: Offerors must provide a basis of estimate for the number of hours or months proposed as well as the labor categories chosen for the work to be performed.
b. MATERIALS: Offerors must provide a basis of the materials proposed and why these materials are necessary for the work to be performed. Include quotations when available. Also provide the rationale that demonstrates how the Offeror determined the costs fair and reasonable.
c. EQUIPMENT: Offerors must provide a basis of the equipment proposed and why each piece of equipment is necessary for the work to be performed. Include quotations when available. Offerors must indicate whether equipment was chosen based on competitive quotes. If equipment was not chosen based on adequate competition, the Offeror must indicate why and provide justification for its selection. Also provide the rationale that demonstrates how the Offeror determined the costs fair and reasonable.

NOTE: Equipment is defined as property having a useful life of more than two years and an acquisition cost of $5,000 or more per unit. Equipment does not include material, real property or special tooling.

d. TRAVEL: Offerors must provide justification for each trip proposed. Include what will be accomplished and explain how each trip benefits DTRA. Trips proposed that benefit the Offeror and/or more than one Government agency under another contract may be subject to cost sharing.

NOTE d.1.: Travel cost estimates should be based on the following:

Except as provided in FAR 31.205-46(a)(3), costs incurred for lodging, meals, and incidental expenses shall be considered to be reasonable and allowable only to the extent that they do not exceed on a daily basis the maximum per diem rates in effect at the time of travel as
set forth in the:

(i) Federal Travel Regulations, prescribed by the General Services Administration, for travel in the contiguous United States,
(ii) Joint Travel Regulation, Volume 2, DoD Civilian Personnel, Appendix A, prescribed by the Department of Defense, for travel in Alaska, Hawaii, and outlying areas of the United States, or the
(iii) Standardized Regulations (Government Civilians, Foreign Areas), Section 925, "Maximum Travel Per Diem Allowances for Foreign Areas," prescribed by the Department of State, for travel in areas not covered in (a)(2)(i) and (ii) of FAR 31.205-46.

NOTE d.2.: DTRA policy does not allow fee to be applied to travel.

e. OTHER DIRECT COSTS (ODC): Offerors must provide a basis of the ODCs proposed and why they're necessary for the work to be performed. Provide quotations or publically posted price lists to support the costs proposed. Also provide the rationale that demonstrates how the Offeror determined the costs fair and reasonable.
f. SUBCONTRACTOR: Offerors must identify which subcontractors were selected based on adequate price competition. For these subcontractors, provide the competitive quotations that support the selection decision. For those subcontractors that were not selected based on adequate price competition, provide the rationale for selection as well as the detailed cost break out and narrative for each subcontractor in accordance with this Attachment.
g. INDIRECT COSTS: Offerors must provide all rates, factors, and bases by year utilized in the development of the proposal and the basis of those rates and factors.
h. FEE: Offerors must provide rationale supporting the fee proposed.

NOTE: Offerors are encouraged to review the factors for how the Government evaluates contractor proposed fee located in DFARS 215.404-71.

THE TABLES OF THE FOLLOWING PAGES WILL BE POSTED TO FEDBIZOPPS AND WILL BE MADE AVAILABLE FOR DOWNLOAD BY THE OFFEROR.

TABLE 1

COST SUMMARY

Cost Element	Base Period			Option I			Option II			Option III		
	Rate Hrly	Quantity # Hrs	Total Amount	Rate Hrly	Quantity # Hrs	Total Amount	Rate Hrly	Quantity # Hrs	Total Amount	Rate Hrly	Quantity # Hrs	Total Amount
Labor Category & Title	$	XX	$	$	XX	$	$	XX	$	$	XX	$
Example: "Material Scientist"	$	XX	$	$	XX	$	$	XX	$	$	XX	$
TOTAL DIRECT LABOR		XX	$		XX	$		XX	$		XX	$
LABOR BURDEN	Rate	Lbr Burden Applied to	Total Amount	Rate	Lbr Burden Applied to	Total Amount	Rate	Lbr Burden Applied to	Total Amount	Rate	Lbr Burden Applied to	Total Amount
FRINGE BENEFITS	%	$	$	%	$	$	%	$	$	%	$	$
OVERHEAD	%	$	$	%	$	$	%	$	$	%	$	$
TOTAL LABOR BURDEN			$			$			$			$
TOTAL MATL/EQUIPMENT			$			$			$			$
TOTAL TRAVEL COSTS			$			$			$			$
TOTAL ALL OTHER DIRECT COSTS			$			$			$			$
TOTAL SUBCONTRACTOR COSTS			$			$			$			$
TOTAL DIRECT COSTS			$			$			$			$
G&A, F&A, FCCM	Rate	Rate Applied to	Total Amount	Rate	Rate Applied to	Total Amount	Rate	Rate Applied to	Total Amount	Rate	Rate Applied to	Total Amount
G&A OR F&A	%	$	$	%	$	$	%	$	$	%	$	$
FACILITIES CAPITAL COST OF MONEY (FCCM) (Attach Completed DD Form 1861)			$			$			$			$
TOTAL COSTS			$			$			$			$
FEE/PROFIT	Fee Rate	Fee Rate Applied to: (total cost, excluding travel &FCCM)	Total Amount	Fee Rate	Fee Rate Applied to: (total cost, excluding travel &FCCM)	Total Amount	Fee Rate	Fee Rate Applied to: (total cost, excluding travel &FCCM)	Total Amount	Fee Rate	Fee Rate Applied to: (total cost, excluding travel &FCCM)	Total Amount
FEE OR PROFIT	%	$	$	%	$	$	%	$	$	%	$	$
TOTAL COST PLUS FEE			$			$			$			$

TABLE 2

MATERIALS							
Item	Manufacturer	Part Number	Unit Price	Quantity	Total Price	Contract Period	Additional Information
Ex: Fiberscope	Company A	1000001	$10,000	2	$20,000	Base Period	List how item pricing was estimated (competitive quotes, established price lists, etc.). If competitive quotes were obtained, provide a copy of those quotes. Provide website link listing item and price if pricing was established based on website pricing.
Ex: Consumables	N/A	N/A	N/A	N/A	$15,000	Option I	

Consumables may be listed as a lump sum if no individual item is over $5,000. For those items that are over $5,000, list separately from the rest of consumable pricing.

TABLE 3

EQUIPMENT							
Item	Manufacturer	Part Number	Unit Price	Quantity	Total Price	Contract Period	Additional Information
Ex: Fiberscope	Company A	1000001	$10,000	2	$20,000	Base Period	List how item pricing was estimated (competitive quotes, established price lists, etc.). If competitive quotes were obtained, provide a copy of those quotes. Provide website link listing item and price if pricing was established based on website pricing.
Ex: Consumables	N/A	N/A	N/A	N/A	$15,000	Option I	

TABLE 4

TRAVEL							
Trip #:		**Location:**				**Contract Period**	
Purpose:						(Select Period)	
Days	**# of People**	**Airfare**	**Per Diem**	**Lodging**	**Other**	**Total**	
						$0.00	

Itemized Expenses for "Other"

Description	**Amount**
Total:	$0.00

Trip #:		**Location:**				**Contract Period**	
Purpose:						(Select Period)	
Days	**# of People**	**Airfare**	**Per Diem**	**Lodging**	**Other**	**Total**	
						$0.00	

Itemized Expenses for "Other"

Description	**Amount**
Total:	$0.00

TABLE 5

OTHER DIRECT COSTS			
Description	Total Price	Contract Period	Additional Information
Example: Laboratory Usage	$20,000	Base Period	List detailed description and additional information stating the need for the requirement and the method with which the total cost was calculated. Example: Twenty hours of laboratory usage is required to complete Task 4 and was calculated at a rate of $200 per hour. Laboratory hours were estimated based on experience with previous efforts of a similar size and scope.

TABLE 6

SUBCONTRACTORS OVERVIEW			
Company Name	Total Price	Contract Period	Additional Information
Company A	$100,000	Base Period	Provide a description of the role of the subcontractor for the effort and how subcontractor pricing was obtained. If competitive procedures were utilized, provide evidence of that competition for comparison.
Company B	$200,000	Base Period	
Company A	$50,000	Option I	

4.4.6. Supplemental Information: The Supplemental Information Volume requires the following information be entered or uploaded:

- Quad charts submitted in Phase I should be updated as necessary and must be re-uploaded to the DTRA website https://www.dtrasubmission.net in Phase II for complete proposal submission. See Section 4.3.2. for Quad Chart format requirements.
- A Statement of Work defining the major tasks and timelines for the effort must be uploaded.
- A brief summary of any proposed Human Subjects research, or a confirmation that the proposed effort does not include Human Subjects research, must be entered.
- A brief summary of any proposed Animal Subjects research, or a confirmation that the proposed effort does not include Animal Subjects research, must be entered.
- A brief summary of any proposed Biosurety and Select Agent research, or a confirmation that the proposed effort does not include Biosurety and Select Agent research, must be entered.
- A statement of any potential Organizational Conflicts of Interest, or a confirmation of no conflicts, must be entered.
- A statement outlining any current and pending support related to the proposed effort must be entered.

4.4.7. Phase II (Full Proposal) Evaluation Criteria: All information and documentation required and necessary for Phase II Proposal evaluation must be contained in the submission. Proposals are encouraged that show a comprehensive approach with citation of supporting fundamental bases (theoretical or experimental data, preference is experimental data) and featuring teaming arrangements with other Service laboratories or Other Governmental Agencies (OGA) that lend unique expertise or specialized facilities to the proposed effort. The evaluation will be based on criteria listed below. The criteria are listed in decreasing order of importance. Criteria are scored on a scale of 1 to 5, with 1 being the highest obtainable score. Weighted calculation is used to derive an overall score that is used as the *basis* of a merit order list to *guide* final funding decisions. Final funding decisions also consider programmatic priorities and are subject to the availability of funds.

4.4.7.1. Scientific and Technical Merit: The objective of this criterion is to assess the extent to which the Offeror has an innovative, unique, high payoff, and comprehensive technical approach based on sound scientific principles. Offerors should demonstrate an understanding of the risks associated with the proposed scientific approach and offers a plan to mitigate those risks or an alternative approach. Offerors must clearly identify the research objective, propose a well-designed approach to address the stated objective, and provide detailed and descriptive background and methods to support the approach. Significant improvements in chemical and biological technology capability above the 'state-of-the-art' are sought.

4.4.7.2. Value to the Joint Chemical and Biological Defense Program Goals: The objective of this criterion is to assess the extent to which the Offeror proposes to answer a basic knowledge question or address an applied/advanced research effort essential to a technology development of interest to the CBDP, and the value of the project deliverable (product, process, answer to basic science question) to the DoD and the general field of research. Offerors must demonstrate a clear knowledge of desired military capabilities and indicate the manner in which the technology will transition. Proposals must demonstrate how the proposed research supports the program goals and responds to the specific topic areas. Offerors must demonstrate that the new technology can be implemented or utilized by end-users as a means to improve their operational capabilities.

4.4.7.3. Capability of the PI and Key Personnel to Perform the Proposed Work: The objective of this criterion is to assess whether the Offeror's team has the requisite expertise, skills and resources necessary to perform the proposed program. This includes an assessment of the team's management construct, key personnel, facilities and past technical experience in conducting similar efforts of the proposed scope. Offerors must demonstrate that their team has the necessary background and experience to perform this project. Facilities should be detailed with discussion of any unique capabilities pertinent to the research.

4.4.7.4. Cost Realism: This objective of this criterion is to establish that the proposed costs are reasonable and realistic for the technical approach offered, as well as to determine the Offeror's practical understanding of the effort. Proposals also will be evaluated for cost justification in relation to the scope of the proposed effort.

4.4.8. Evaluation Results: Notification of acceptance of Phase II proposals with intent to fund will be sent to Offerors via e-mail and available on the DTRA proposal submission website https://www.dtrasubmission.net upon finalization of Phase II evaluations. A summary of the Government's evaluation will be made available to Offerors via the DTRA proposal submission website. Funding of selected projects is subject to availability of funds.

5.0. Funding

Phase I Pre-proposals and Phase II Proposals for new projects starting in FY14 and spanning up to three years will be accepted.

Multiple year funding will depend on availability of funds and adequate demonstration of progress toward program objectives. Funding/continuation decisions will be made on an annual basis.

6.0. Licensing and Contractual Agreements

Intellectual Property, Cooperative Research and Development Agreements (CRADAs), Materiel Transfer Agreements (MTAs), or other contractual arrangements which maximize DoD's access to novel new or existing technologies, and reduce research costs, are encouraged. Licensing and contractual agreements should be clearly outlined in the Phase I and Phase II Proposals. The Government's intellectual property rights to products with potential chemical, biological and radiological defense applications should be clearly addressed in the submissions.

7.0 Milestone Schedule

Action / Milestone	Date
FY14/16 Solicitation Released (Pre-Proposal / Phase I begins)	20 February 2013
Pre-Proposal / Phase I Submission Deadline	20 March 2013 -- NLT 1400 ET
Invitations for Full Proposal Sent (Proposal / Phase II begins)	2 April 2013
Full Proposal / Phase II Submission Deadline	14 May 2013 -- NLT 1400 ET
Proposal Decisions Released	On or About 11 June 2013
Funding Provided	Subject to Availability of Funds, January 1, 2014

8.0 Points of Contact

Questions regarding the content of this solicitation or proposal submission requirements should be directed to CB-FY14-16BAA@dtra.mil.

Technical questions regarding the DTRA proposal submission website should be directed to the Help Desk at 800-947-4192, help@dtrasubmission.net.

APPENDIX A

INFORMATION SYSTEMS CAPABILITY DEVELOPMENT DIVISION

TOPIC AREA FUNDING OPPORTUNITIES

PROPOSAL TOPICS

The Information Systems Capability Development Division seeks new initiatives in response to select topics applicable to Advanced Warning, Analysis and Reporting, Systems Analysis and Planning, and Systems Biology and Bioinformatics capability areas.

Chemical and Biological Effects Manual Number 1 – Chapter Development

Topic: CBI-01

A. Background:
The Chemical and Biological Agent Effects Manual Number 1, or CB-1, is intended to capture the phenomenology, data, and methods used in chemical and biological (CB) defense for research, development, test, and evaluation and to break down barriers to information sharing, critical to the advancement of future technology solutions. CB-1 is intended to have the relevance and utility to the CB defense community that DTRA's publication, "Capabilities of Nuclear Weapons: Effects Manual No. 1 (EM-1)" has had to the nuclear/radiological community. EM-1 is the authoritative source on nuclear weapons phenomenology and effects, and is used government-wide. Its primary function is to promulgate to the military services and their contractors an official authoritative position on nuclear weapons phenomena and their effects on military systems. For researchers, EM-1 summarizes the current knowledge of these phenomena, and is therefore "the primary source document" from which new R&D programs may spring. DTRA J9-CB is developing CB-1 to provide a similarly valuable resource for CB defense analysis.

B. Objective:
DTRA seeks proposals from organizations with extensive subject matter expertise in one or more selected topics related to CB defense to utilize that expertise to craft individual chapters of CB-1. Respondents to this topic should have unique and extensive expertise in one or more of the following topics, as they pertain to CB Defense: Structures/Site Characteristics, Medical Diagnostics (biological and/or radiological agent diagnostics only), Medical Protection (biological and/or radiological protection only), Consequence Assessment, Consequence Management, Battlespace Management, and Reconnaissance. Chapter definitions are included below. Note that proposals for only the chapters or subchapters explicitly named above are being sought. All other chapters and subchapters of CB-1 are already in development.

Chapter 8: Structures, Site Characteristics – The Structures, Site Characteristics Chapter should evaluate methods and data used to describe buildings (structures and protective measures) and site attributes (interior and exterior) used for hazard prediction, battlespace management, contamination avoidance and collective protection. Subtopic areas may include, but are not limited to: (1) 3D internal/external building

representations, (2) infrastructures (e.g., doors, windows, ducts/HVAC systems), (3) building materials, and (4) protective measures (e.g., dampers, fans, sensors, filters).

Chapter 10: Medical Diagnostics – Medical diagnostics deals with the diagnosis of infection by or exposure to bacterial, viral, or toxin agents (biological diagnostics) or of exposure to nerve, vesicants, respiratory, and blood agents (chemical diagnostics). The Medical Diagnostics Chapter should assess methods and data used to support rapid detection and diagnostic assays development for threat agents and the evaluation/ determination of applicability of new technologies to diagnostics in a warfighting environment. There may be distinct and separate subsections for chemical, biological, and radiological diagnostics. Subtopic areas for biological may include, but are not limited to: (1) assay development, (2) identification of novel biomarkers, (3) test and evaluation, and (4) genetically engineered threats. (Note: proposals to develop the subchapter for chemical agent diagnostics are not being solicited. Only proposals for developing the biological and/or radiological subchapters of this chapter are being solicited.)

Chapter 11: Medical Protection – The Medical Protection Chapter should assess methods and data used to provide medical protection and prevention to preserve fighting strength (medical prophylaxes and pretreatments), and medical management of CB casualties and post-exposure capabilities to enhance survivability, expedite and maximize return to duty (therapeutics). Vaccines and chemical pretreatments and protectants can be administered before exposure to provide both specific and broad-spectrum protection against validated chemical or biological agents. Therapeutics (medical treatments and pharmaceuticals) can be administered after exposure to a chemical or biological agent, mitigate or curtail the effects of that exposure and sustain forces operating in a Chemical Biological Warfare (CBW) hazard area. There may be distinct and separate subsections for chemical, biological, and radiological protection. Subtopic areas for pretreatments may include, but are not limited to: (1) multi-agent vaccine development, (2) vaccine research support (proteomics, genomics, and bioinformatics), (3) vaccine technology development, and (4) CWA pretreatments (e. g. bio-scavengers). Subtopic areas for therapeutics may include, but are not limited to: (1) bacterial, (2) viral, (3) toxin, (4) chemical agent therapeutics, (5) low-level Chemical Warfare Agent (CWA) exposure-effects and countermeasures, and (6) nontraditional nerve agents. (Note: proposals to develop the subchapter for chemical agent protection are not being solicited. Only proposals for developing the biological and/or radiological subchapters of this chapter are being solicited.)

Chapter 13: Consequence Assessment – Consequence assessment is defined as an assessment of the consequences of the use of weapons of mass destruction or the purposeful or inadvertent release of chemical or biological agents or radiological material and substances. Consequence assessment is sometimes used as a general name for typical applications in which Atmospheric Transport and Dispersion (ATD) models are employed to quantify and evaluate the likely consequences (or negative impacts) from varying CBRN threats with a range of scenarios. This can be quantified in terms of fatalities, casualties, or physical damage. Subtopic areas may include, but are not limited to: (1) the integration of T&D predictions with human effects and population databases/models to compute casualty estimates.

Chapter 14: Consequence Management – Consequence management deals with those measures taken to protect public health and safety, restore essential government services, and provide emergency relief to governments, businesses, and individuals affected by the consequences of a CBRN situation. The Consequence Management Chapter should assess methods and data used to perform forensics, provide health care, and conduct operational and medical/material management during an emergency event. Subtopic areas may include, but are not limited to: (1) Standard Operating Procedures (SOPs) and on-scene checklists (evidence collection, investigative procedures, and general response).

Chapter 15: Battlespace Management – Battlespace management deals with the dynamic synchronization (planning and monitoring) of all battlespace activities, both military and non-military. The Battlespace Management Chapter should assess methods and data used to provide an operational context for intelligent automation and support for command decision-making. (Operational context is the sum of battlespace operational planning and execution knowledge, information and data, plus the real-time tactical picture). The Common Operational Picture 1 (COP), many elements of which are typically included in Operations Plan/Orders/Tasking (OPPLAN/OPORD/OPTASK) messages, provides the commander with "operational context" (or situational awareness), information such as: the scope of operations, missions, commander's intent, Rules of Engagement (ROE), command relationships, task force order of battle, courses of action, tasking, coordination guidelines, schedule of operations, communication plans, battlespace management, sensor management plans, threat assessment, and environmental forecasts and prediction guidance. Subtopic areas may include, but are not limited to: (1) execution support (TTP's, CONOPs, checklists), and (2) CBRN messages.

Chapter 16: Reconnaissance – The Reconnaissance Chapter should address methods and data used to support operations to include contamination surveys, agent/material sampling, and casualty search and extraction. CBRN reconnaissance is critical to the mission of contamination avoidance providing information about CBRN hazards within an area of operations for command-level decision making. Usually five critical tasks are performed: sampling, detecting, identifying, marking and reporting. Subtopic areas may include, but are not limited to: (1) fielded and production vehicle systems, and (2) casualty evacuation.

Individual proposals should consist of a strategy for aggregating, organizing, and documenting all validated methods and data pertinent to analysis within the particular chapter as well as developing tutorial-level documentation of how those tools are exploited for defense against CB agent warfare. All included data must have pedigree recognized by the CB Defense Program (CBDP) and a standard method should be identified and described by which future revision or addition to the data may be made. The effort should result in an optimal, current, curated aggregation of data and methods for use by the CBDP. Raw data should be consolidated and determination will be made of its acceptability and utility for CB defense analyses. Metadata must be defined as appropriate and must sufficiently contextualize the validity and applicability of all data and methods included. All products must be compatible with the CB-1 central database currently under development. This will be achieved by allowing some flexibility in the proposal for the Offeror to communicate planned chapter contents to the DTRA COR, to receive guidance on organization and format, and to act on that guidance. The chapter should consider the entire breadth of the subject. Therefore, the Offeror will need to bring sufficient expertise to properly develop a complete chapter. This may be accomplished through subcontracts with other organizations. Conversely, an effort too heavily dependent on subject matter expert time will likely be very inefficient, so the Offeror will need to utilize a mix of skillsets to ensure that the best possible product will be developed in the most efficient manner. The mix of writers, researchers, and subject matter experts necessary to accomplish this may be different for each topic. A smaller topic might require 1 or 2 of each skillset, while a larger topic might require several of each.

The final deliverable will consist of the correctly organized and formatted chapter and any associated data. These will all be provided to the DTRA COR. Note: Much of the data related to chapter contents will be owned or kept by external organizations. In such cases, CB-1 will provide a detailed description of the data and how it can be used for relevant CB defense analysis. For example, a technical report held by the Chemical, Biological, Radiological and Nuclear Defense Information Analysis Center (CBRNIAC) will be referenced in

CB-1 with instructions facilitating use of the data within the report. The report will physically remain at CBRNIAC.

In addition to proposals focused on chapter development, DTRA will also consider proposals relevant to providing an efficient framework for CB-1 through innovative methods for the storage and access of chapter content within the Defense Threat Reduction Information Analysis Center (DTRIAC) Next Gen Scientific and Technical Information Archival and Retrieval System (STARS) framework.

C. Program Milestones and Metrics:
CB-1 overall production is articulated into several years of effort, but promising individual proposals would likely span 2 to 3 years. Each proposal should focus on a single chapter or subchapter comprehensively covering a single topic from the list above. In areas where two or more topics overlap, proposals should include some flexibility to allow for coordination with other chapter developers. Resolution of the most effective organization of a chapter (i.e., determination of to which chapter an overlapping area will belong and therefore which developer will be responsible for writing it) will be made by the DTRA COR. In any case, each chapter should be developed uniquely in a manner that most appropriately suits the material, while maintaining the general organization and tenor of the overall CB-1 product. Each chapter should essentially stand alone as comprehensive tutorial on the topic, with references across chapters and into other sources as necessary. DTRA must be consulted regularly on chapter content, and the DTRA COR will help to coordinate review by external subject matter experts as necessary. The DTRA COR will facilitate communication between performers to ensure the most effective overall organization and representation of data. Required datasets should be made suitable for inclusion into the CB-1 central database. This will require substantial coordination with the DTRA COR. Such databases will be referenced and described in detail in the chapter being developed.

Program Milestones:
Year 1: Outline chapter for approval by DTRA COR, very early in the first year.
Years 1+: Proposal should include milestones for completing individual subchapters, dependent largely on the volume and diversity of information to be collected in each.
Final Year: Complete and deliver entire chapter to DTRA COR, including any data not externally managed. Proposal should also include milestones for consulting with DTRA personnel (the COR and other SMEs at DTRA) throughout chapter development.

Program Metrics:
Development of each chapter will require a unique timeline, depending largely on the volume and diversity of data involved. Though initial outlines may be included in a proposal, extensive consultations with the DTRA COR and other SMEs are expected to take place before an outline is approved. The success of a chapter development effort should depend on DTRA COR approval of the chapter outline, DTRA COR approval of individual subchapters, and completion of the chapter by the end of the period of performance.

APPENDIX B

TRANSLATIONAL MEDICAL DIVISION

TOPIC AREA FUNDING OPPORTUNITIES

PROPOSAL TOPICS

Adaptive Medical Countermeasures and Technologies Biological Pretreatments

Objective: Defeat chemical and biological threats to the warfighter and nation through translational medicine (SHIELD and SUSTAIN mission capability and health)

To reach this goal, proposals that characterize and evaluate novel candidates against specified threat agents and address the topics presented below are desired. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks.

Topic: CBM-01
Novel vaccines directed against *Burkholderia pseudomallei* and *Burkholderia mallei*.

Background *B. pseudomallei* is a gram-negative bacterial pathogen that causes Melioidosis, a disease endemic in Southeast Asia and northern Australia. Melioidosis is historically associated with a high mortality rate due to the speed with which septicemia develops and the inherent resistance of the bacteria to several classes of antibiotics. For example, a 20-year prospective study of Melioidosis in northern Australia found an overall mortality of 14 percent and a 50 percent mortality rate for patients with septic shock. A 9-year prospective study of Melioidosis in northeast Thailand found an overall mortality rate of 42.6 percent. Prolonged courses of antibiotics are required to treat Melioidosis. Despite prolonged antimicrobial therapy, recurrent disease is common (at a rate of greater than or equal to 6 percent in the first year). In addition to the public health threat posed by naturally occurring infections, *B. pseudomallei* have been determined to pose a material threat sufficient to affect the United States' national security.

B. mallei (formerly Pseudomonas mallei) are a gram-negative, bacterial pathogen that causes Glanders and is primarily a zoonotic disease in Africa, Asia, the Middle East, and Central/South America. Natural Glanders infections occur primarily in horses, donkeys, and mules, but most mammals have some degree of susceptibility. While human susceptibility to *B. mallei* infection has not been studied in depth, the organism is highly infectious in the laboratory setting. Prolonged antimicrobial therapy is required to treat B. mallei infection and prevent its relapse. *B. mallei* has also been determined to pose a material threat sufficient to affect the United States' national security.

Because of the lengthy antibiotic therapy required to treat Melioidosis and Glanders and the suboptimal clinical outcomes, lack of vaccines, possible biothreat applications, and public health implications, there is significant interest in developing new MCMs as well as improved animal models to evaluate candidate MCMs for these diseases.

Impact: This topic will support CBD Program goals by providing early-stage vaccine candidates against Meliodosis and/or Glanders with the potential for use with agile bio-manufacturing technology for rapid advanced development. This will provide (1) candidate vaccines that could be further tested for safety and efficacy in pre-clinical and clinical trials and (2) fundamental information regarding protective immunity against *Burkholderia pseudomallei* and *Burkholderia mallei*. This work may also require the development of a non-human primate model of infection for evaluation of future Medical Countermeasures.
Objectives: Proposals are sought to develop innovative vaccine candidates and/or novel vaccination strategies and platforms using protective antigens derived from *Burkholderia mallei* and *Burkholderia pseudomallei*. Testing and evaluation should examine the immunogenicity and efficacy in small animals challenged with ***inhalation*** *Burkholderia mallei* and *Burkholderia pseudomallei*. Ideally, candidate vaccines must be able to elicit a robust and effective pathogen-specific humoral and cellular immune response pProposals utilizing a form of inhalation challenge will be considered at a higher priority. Examples of inhalation routes are ranked below in terms of high priority to low priority:

1) Aerosol;
2) Intra-tracheal (IT) via hand held microsprayer;
3) Intra-tracheal (IT);
4) Intra-nasal (IN).

Protection should be demonstrated against both species of *Burkholderia* documented to be pathogenic to humans, although protection against a single species would be considered as initial proof-of-concept. Whole cell vaccine candidates (i.e., heat/chemically killed, live attenuated, whole cell lysate etc.) and un-conjugated LPS used solely as a vaccine candidate will be considered, although at a low priority. Protective antigens derived from *Burkholderia mallei* and *Burkholderia pseudomallei* expressed or attached on an existing or novel platform will be considered. Proposals amenable to use in flexible, single-use, advanced development and bio-manufacturing techniques will be viewed favorably. Proposals utilizing *Burkholderia spp.* challenge agents from the following list will be considered at a higher priority:

1) *Burkholderia pseudomallei* – MSHR305
2) *Burkholderia pseudomallei* – 406e
3) *Burkholderia pseudomallei* – MSHR668
4) *Burkholderia pseudomallei* – 1106a
5) *Burkholderia pseudomallei* – K96243
6) *Burkholderia pseudomallei* – 1106a
7) *Burkholderia pseudomallei* – 1026b
8) *Burkholderia mallei* – 23344 FMH

Topic CBM-02

Vaccine Candidates for Type A Francisella tularensis

Background: *Francisella tularensis* is one of the most infectious human respiratory pathogens. Inhalation of as few as 10 organisms can cause a highly debilitating disease with an estimated mortality rate of over 30% in untreated patients. Given its potential to severely reduce the warfighting capabilities of the armed forces and to inflict psychological trauma on the civilian population, *F. tularensis* was previously developed as a biological weapon and remains a serious bioterrorism threat today. Prophylactic vaccination is the best countermeasure against this threat; however, there is currently no approved vaccine for this purpose however, there is good

historical evidence that humans can be vaccinated against respiratory tularemia. Currently, the most effective vaccine is an attenuated live vaccine strain of Type B *Francisella tularensis* designated as LVS. LVS is only given to at-risk military and laboratory personnel through the Special Immunization Program at USAMRIID and it is unlikely to be licensed for mass vaccination because its mechanism of attenuation has not been defined. The safety concerns are well-founded because recent data showed that reintroduction of virulence genes restored some virulence to LVS. Moreover, LVS vaccination has been associated with significant adverse effects for some individuals. With the continued threat of weaponization, the need for a new generation of defined tularemia vaccines is greater than ever.

Impact: This topic will support CBD Program goals by providing early-stage vaccine candidates and platforms against Type A *Francisella tularensis*. This will provide (1) candidate vaccines that could be further tested for safety and efficacy in pre-clinical and clinical trials and (2) fundamental information regarding protective immunity against *F. tularensis*.

Objectives: Proposals are sought to develop innovative vaccine candidates and/or novel vaccination strategies and platforms using protective antigens derived from Type A *Francisella tularensis*. Testing and evaluation should examine the immunogenicity and efficacy in small/large animals challenged with *inhalation* Type A *Francisella tularensis* SCHU S4. Ideally, candidate vaccines must be able to elicit a robust and effective pathogen-specific humoral and cellular immune response. Proposals utilizing a form of inhalation challenge will be also be considered at a higher priority. Examples of inhalation routes are ranked below in terms of high priority to low priority:

1) Aerosol;
2) Intra-tracheal (IT) via hand held microsprayer;
3) Intra-tracheal (IT);
4) Intra-nasal (IN).

Vaccines derived from LVS, rationally attenuated mutants of LVS or Type A *Francisella tularensis* SCHU S4, along with other whole cell-based vaccination strategies (i.e., heat/chemically killed or whole cell lysate etc.) will not be considered. Protective antigens derived from Type A *Francisella tularensis* expressed or attached on an existing or novel platform will be considered. Proposals which outline efficacy testing must utilize Type A *Francisella tularensis* SCHU S4 as a challenge agent using the inhalation routes described above. Additionally, the animal models to be used for the evaluation of efficacy resulting from vaccination are:

1) F344 Rat
2) *Cynomolgus macaque*

Offerors are expected to pair with institutions which have the capability to utilize these models using the routes of challenge outlined above. Proposals amenable to use in flexible, single-use bio-manufacturing techniques will be viewed favorably.

Additionally, proposals may involve vaccine platforms being developed at any stage of technological maturity and include any or all of the following:

1. Discovery and/or incorporation of protective antigens
    - *In silico* approaches to determine likely immunogenic motifs
    - *In vitro* evaluation of immunogenicity

- *In vivo* testing of immunogenicity and potential efficacy
- Incorporation of relevant antigens into vaccine platforms

2. Comparative approaches to determine optimal delivery platforms and/or dosing strategies in the mouse model
   - Comparisons of the same antigen(s) on multiple platforms to determine the optimal delivery vehicle
   - Comparisons of the same antigen(s) and platform on various dosing strategies
   - Optimization of adjuvant formulation
3. Evaluation of vaccine candidate efficacy in appropriate animal model
   - Identification of correlates of protective immunity in the infection model
   - Assay development for immune correlates
   - Initial screening of a lead vaccine candidate

Topic: CBM-03

Vaccine Candidates for Q Fever

Background: *Coxiella burnetii* is a gram negative bacterium that is prevalent worldwide and causes Q Fever. The disease is typically spread via aerosol exposure to tissues from infected animals and can manifest in both acute and chronic phases. Antibiotic treatment is the current standard of care in most countries, but the typical symptoms are non-specific, complicating the ability to diagnose and treat in a timely manner[1]. For acute Q fever, doxycycline is the recommended antibiotic; chronic Q fever can require both doxycycline and hydroxychloroquine over a course of several months or years. Importantly, Q Fever is a general threat to Warfighter health as it has been diagnosed in U.S. Warfighters returning home from deployments in the Middle East[2]. However, it is also considered to be a biological threat, largely due to its robustness in terms of resistance to heat, ultraviolet light, and other environmental factors. Furthermore, recent advances in culturing *C. burnetii*[3] may facilitate access to this agent, genetic manipulation, and the growth of large quantities. Due to the above issues, vaccination against Q Fever may be a desirable option for Warfighters who may be exposed to *C. burnetii*. Australia has licensed a formalin-inactivated vaccine (Q-Vax) against Q Fever, but this has experienced significant side effects (swelling, erythema, and in some cases headaches and flu-like symptoms) and requires a pre-vaccination skin test for sero-positivity[4]. Therefore, alternative strategies to vaccination are needed.

Impact: This topic will support CBD Program goals by providing early-stage vaccine candidates with platforms against Q Fever. This will provide (1) candidate vaccines that could be further tested for safety and efficacy in pre-clinical and clinical trials and (2) fundamental information regarding protective immunity against *C. burnetii*. This work may also require the development of a non-human primate model of infection for evaluation of future Medical Countermeasures.

Objectives: The overall objective of this topic is to discover candidate vaccines that are effective against *C. burnetii* and proceed to develop lead candidates for further testing in animal models and clinical trials. Proposals may involve vaccine platforms being developed at any stage of technological maturity. Research in this area may include any or all of the following:

1. Discovery and/or incorporation of protective antigens
   - *In silico* approaches to determine likely immunogenic motifs
   - *In vitro* evaluation of immunogenicity
   - *In vivo* testing of immunogenicity and potential efficacy

- Incorporation of relevant antigens into vaccine platforms

2. Comparative approaches to determine optimal delivery platforms and/or dosing strategies in the mouse model
   - Comparisons of the same antigen(s) on multiple platforms to determine the optimal delivery vehicle
   - Comparisons of the same antigen(s) and platform on various dosing strategies
   - Optimization of adjuvant formulation
3. Development of a non-human primate model of aerosol *C. burnetii* infection
   - Determination of the LD_{50} and conduct of natural history studies
   - Identification of correlates of protective immunity in the infection model
   - Initial screening of a lead vaccine candidate

Proposals amenable to use in flexible, single-use bio-manufacturing techniques will be viewed favorably.

[1]D. Raoult, et.al. (1995) Q Fever. *Clinical Infectious Diseases*. 20(3): 489-495.
[2]J.D. Hartzell, et.al. (2007) Atypical Q Fever in US Soldiers. *Emerging Infectious Diseases.* DOI: 10.3201/eid1308.070218.
[3]A. Omsland, et.al. (2009) Host cell-free growth of the Q fever bacterium Coxiella burnetii.. *PNAS.* 106(11): 4430-4434.
[4]P.C.F. Oyston, et.al. (2011) Q Fever: the neglected biothreat agent. *Journal of Medical Microbiology*. 60:9-21.

Topic: CBM-04
Vaccine Candidates for Brucellosis

Background: Brucella is a genus of Gram-negative bacteria, one of the world's most important veterinary diseases, and is zoonotic. Mortality is low but the disease in humans can be prolonged and incapacitating. The organism is transmitted by ingestion of infected food (e.g., unpasteurized milk products), direct contact with fluids from infected animals (especially sheep, cattle, pigs), and inhalation of aerosols containing the bacteria, which makes it a possible agent of biological warfare. Brucellosis is only rarely transmitted between humans. The minimum infectious dose is 10 – 100 organisms.[1] The organism was isolated from British soldiers dying of Malta fever (*Brucella melitensis)* during the Crimean War. Currently there are an estimated 500,000 cases of human brucellosis annually and laboratory acquired brucellosis is common. Brucellosis can debilitate warfighters. It resembles several non-specific febrile diseases and, in deliberate aerosolized form, could lead to more rapid onset of disease and delayed diagnosis. A 2-4-week latency period precedes onset of acute undulating fever (>90% of all human cases).[2] Later complications may include fatal endocarditis. Bacteria persist in the mononuclear phagocyte system, including the spleen, liver, lymph nodes and bone marrow and can be isolated from the blood. Treatment requires a 6-week course of rifampicin and doxycycline and a high rate of side effects has been reported. Although two modified live vaccines are used in cattle and bison (strain 19 and RB51) there is no FDA-approved vaccine for people.

Impact: This topic will help reach CBD Program goals by providing (1) early-stage vaccine candidates and platforms against Brucella melitensis and B. abortus that could be further tested for safety and efficacy in pre-clinical and clinical trials and (2) fundamental information regarding protective immunity against *Brucella species.*

Objectives: The overall objective is to discover candidate vaccines and platforms that prevent human infection and/or disease caused by *Brucella melitensis* and *B. abortus* for selection of lead candidates for further testing in animal trials to gain FDA licensure and use in at-risk warfighters. The ideal candidates will elicit an effective,

specific, humoral and cellular immune response with minimal local or systemic inflammation. Proposals may involve vaccine platforms being developed at any stage of technological maturity. Research in this area should include any or all of the following:

- Discovery and/or incorporation of protective antigens
  - *In silico* approaches to determine likely immunogenic motifs
  - *In vitro* evaluation of immunogenicity
  - Incorporation of relevant antigens into vaccine platforms
  - *In vivo* testing of immunogenicity and potential efficacy - challenged with oral or inhaled *Brucella sp.*
- Comparative approaches to determine optimal delivery platforms and/or dosing strategies in the mouse model
  - Comparisons of the same antigen(s) on multiple platforms to determine optimal delivery vehicle
  - Comparisons of the same antigen(s) and platform on various dosing strategies
  - Optimization of adjuvant formulation
- Development of the most appropriate animal model for human aerosolized infection with *Brucella sp.*
  - Determination of the LD_{50} and conduct of aerosol *Brucella* infection
  - Identification of correlates of protective immunity in the infection model
  - Initial efficacy and safety screening of a lead vaccine candidate
- Opsonin-based post-exposure prophylaxis for Brucella melitensis or B. abortus in humans.
  - Small molecules that bind and coat bacteria for clearance by monocyte-macrophage system or antibody-dependent cell-mediated cytotoxicity.
- Proposals amenable to use in flexible, single-use bio-manufacturing techniques will be viewed favorably.

1. USAMRIID's Medical Management of Biological Casualties Handbook, 4th Edition, Fort Detrick, Frederick, MD., February 2001
2. http://www.vetmed.wisc.edu/pbs/zoonoses/brucellosis/brucellosishuman.html
3. Hagan and Bruner's "Microbiology and Infectious Diseases of Domestic Animals", 8th Edition. Cornell University Press, Ithaca, NY. 1988.

E*merging Infectious Diseases*. 2012 Jan. http://dx/doi/org/10.3201/eid1801.AD1801

Topic: CBM-05
Drug Discovery and Development of Therapeutics for Encephalitic Alphavirus Infections

Purpose:
This topic seeks milestone-driven proposals focused primarily on the discovery of novel small molecule therapies for the alphaviruses of greatest concern to the DoD Joint Chemical and Biological Defense Program (i.e. VEEV, EEEV, and WEEV). The ultimate goal of the program is to deliver at least one lead and one backup chemical series effective against alphaviruses as identified through *in vitro* and pre-clinical animal challenge models. Compounds active *in vitro* will progress through a methodical medicinal chemistry campaign to establish the pharmacophore and to build SAR on biotargets, *in vitro* ADME, and safety properties to, in turn, enable the selection of compounds for pharmacokinetics, toleration, and biomarker-driven *in vivo* efficacy and safety studies. In the best scenario, the project would identify a superior compound or series with clear intellectual property that could be later optimized for advanced pre-clinical testing. Responsive proposals will focus on and will include preliminary data and down selection criteria for drugability establishing proof-of-

concept for candidate products towards a defined Target Product Profile (that will be submitted at the Phase II stage). Clinical trials will not be supported under this topic.

Background:
Select alphaviruses can cause severe disease in humans and represent a significant threat to public health. Venezuelan (VEEV), eastern (EEEV), and western equine encephalitis (WEEV) viruses, are causative agents of debilitative, acute, and sometimes fatal encephalitis in North, Central, and South America. These alphaviruses are naturally maintained in a zoonotic cycle between nonhuman vertebrate hosts and mosquito vectors. Natural human cases are rare and occur through the bite of an infected mosquito. VEEV, EEEV, and WEEV are of interest to the biodefense community, based on historical weaponization programs, ease of genetic manipulation and high-titer production, stability, and ability to infect by aerosol route. Given this threat, there is a critical need for anti-alphavirus therapeutic(s) effective against VEEV, EEEV, WEEV, or all three. Currently, there are no licensed drugs available for the treatment of VEEV, EEEV, WEEV infections. This represents a significant capability gap in the DoD Joint Chemical and Biological Defense Program's research program.

Alphavirus virions are small, spherical particles with a nucleocapsid core surrounded by a host-derived lipid membrane. The nucleocapsid is composed of the viral capsid protein (C). Glycoprotein spikes, composed of trimers of viral E1/E2 heterodimers are embedded in, and extend from the viral membrane. During the virus lifecycle, four viral non-structural proteins (nsPs) are also expressed and are responsible for viral transcription and genome replication. The capsid protein and nsPs are thought to be attractive targets for antiviral drug development.

This BAA topic supports establishment of small-molecule therapeutic discovery programs that are focused primarily on single or multiple specific and known viral protein targets. To date, most alphavirus research has utilized the prototypic Old World alphaviruses, Sindbis virus (SINV), and Semliki Forest virus (SFV). Enzymatic activities have been defined for the capsid protein and the nsPs in at least one alphavirus. However, in many cases these protein functions have not been confirmed in VEEV, EEEV or WEEV proteins. Such experiments are necessary to enable assay development and drug discovery efforts relevant to this solicitation. Alphavirus non-structural proteins and the capsid protein will be acceptable targets. Types of screens that may be developed include *in vitro* biochemical screens based on a known enzymatic activity of an alphavirus protein. Likewise, protein-protein interactions (viral-viral), or viral protein post-translational modifications may be targeted while protein-protein interactions between the virus and host are not the primary focus of this topic. *In silico* tools for quantitative pharmacophore development or structure-based design are encouraged. Coordinates for a VEEV protease nsP2 crystal structure are available. However, proposals that clearly outline a starting point for chemical matter and utilize an experiment-driven, chemistry approach with a solid screening methodology for VEEV, EEEV, or WEEV will be given priority.

Requirements:
The ultimate goal of the program is to support the discovery of novel antiviral compounds through proof-of-concept small animal studies with potential follow-on work further examining the development-readiness of a compound or compound series. It is envisioned that projects will include the following components spread over the course of several years.
Biology and Chemistry
These studies are focused on establishing VEEV, EEEV, or WEEV proteins as targets for antiviral drug development efforts. Programs may include characterization/confirmation of enzymatic activity, structure determination, and assay development and identification and optimization of small molecules from multiple, distinct series that effectively inhibit defined alphavirus protein activities, as demonstrated in a VEEV, EEEV,

or WEEV cell-based assays. Antiviral activity against two or more of these species is desirable, but not required. Furthermore, a strategy that circumvents or limits the development of drug resistance would be highly desirable.

Preliminary Chemical Matter

An initial source of chemical matter (e.g. literature, patents, substrate analog, etc) should be provided to show that there is a clear path forward on designing or procuring a control inhibitor that will serve to validate the cell-based screens. For example, peptidomemetics or peptide-based suicide inhibitors have been described for various virus proteases. Reviewing the available data may also enable the capture of SAR and identify compounds with untapped intellectual property. Chemical library screening is acceptable for finding leads, but the size, curation, documented stability, diversity, and chemical complexity of any library should be weighed carefully against the drug target. Some rationale for initial lead-seeking should be included.

In vitro ADME and PK

Hits from primary pharmacology screens will undergo *in vitro* ADME screening and assessment of blood-brain barrier permeability in a rodent model to enable selection criteria for *in vivo* studies. Drug transporter flux studies may prove helpful in driving SAR when unbound drug concentrations in the brain are lower than needed. Stability or absorption/penetration properties in *in vitro* or *ex vivo* models are encouraged. Pharmacokinetic studies of lead compounds will be conducted in rodents to confirm biopharmaceutical properties and drug disposition and to enable dose selection for efficacy studies.

Pharmacology

These studies are focused on investigation of *in vivo* efficacy of lead candidates in small animal models of VEEV, EEEV, and/or WEEV infection. The dosing regimen should be chosen to give systemic unbound plasma and brain drug concentrations in the animal that are some multiple above the unbound *in vitro* inhibition constant for the test compounds. A dose-titration biomarker (e.g. systemic and brain tissue viral RNA) study with proper controls should be conducted for selected active compounds to establish a desirable preliminary PK/PD relationship.

Safety and Toxicology

Animal toleration of test compounds and any atypical formulation vehicles will be evaluated. Toleration should encompass the doses and duration of proposed efficacy studies, and clinical pathology should be considered. Further *in vitro* (e.g. cellular tox, genetox, Ames, bioactivation, hERG inhibition, CEREP secondary pharmacology screening) and *in vivo* toxicology studies may be pursued as promising compounds progress to obtain an early read on an estimated safety margin.

Important characteristics of successful proposals for this topic include the following:

Each proposal may target a known viral protein(s) and must utilize an experimental SAR-driven medicinal chemistry effort to identify and optimize chemical series.

For library screening and *in silico* structure-guided drug design, priority is given to performers with established expertise in this area. Utilization of industry partners, research organizations, or dedicated academic high-throughput screening centers is encouraged.

Outlining a logical screening funnel with an overview of how experiments and metrics will be used to translate *in vitro* findings to *in vivo* effects, would build investigator credibility.

Offerors must include clear and quantitative go/no go decision points

This topic is primarily interested in discovery and development of small molecule therapeutics targeting viral proteins. Proposals focused on the following will be reviewed, but should focus on development of more mature candidates with compelling data provided demonstrating efficacy against VEEV, EEEV, and/or WEEEV.

1. Development of therapies that target a host protein

2. Nucleic acid (i.e. siRNA, antisense) therapies
3. Antibody-based therapies
4. Protein or peptide-based therapies
5. Phage-based therapies

The following are considered outside of the scope of the topic.

1. Identification of host proteins that play a critical role in the virus lifecycle (host target ID)
2. Efforts relying too heavily on SINV and SFV as model systems
3. Clinical trials

Topic: CBM-06
Antimicrobial Development for *Burkholderia pseudomallei* and Multi-Drug Resistant (MDR) Strains of *Bacillus Anthracis, YersiniaPestis,* and *Francisella Tularensis*

Purpose:

This topic seeks milestone-driven proposals focused on the discovery and development of novel small molecule or peptide antimicrobial therapies for *Burkholderia pseudomallei* and multi-drug resistant (MDR) strains of *Bacillus anthracis, Yersinia pestis*, and *Francisella tularensis*. The ultimate goal of the program is to rapidly deliver small molecule or peptide inhibitor(s) effective against either *B. pseudomallei* and/or MDR strains of *B. anthracis, Y. pestis*, and *F. tularensis* ideally culminating in an Investigational New Drug (IND) submission that qualifies the product for progression to clinical Phase I clinical studies. Responsive proposals will focus on either *Burkholderia pseudomallei* and/or multi-drug resistant (MDR) strains of *B. anthracis, Y. pestis*, and *F. tularensis* and will include preliminary data establishing proof-of-concept for candidate products towards a defined Target Product Profile (that will be submitted at the Phase II stage). Clinical trials will not be supported under this topic.

Background:

In the case of a potential biological attack, the military must be prepared to defend against traditional bacterial threat agents in addition to strains with natural and/or engineered resistance to one or more classes of available antibiotics. Although there are a number of FDA approved drugs that are available to treat *B. anthracis, Y. pestis*, and *F. tularensis* including ciprofloxacin, doxycycline, gentamicin, and others, there is potential for naturally emergent or engineered resistance to these antibiotics rendering them ineffective against these organisms. In addition, many strains of bacteria have evolved resistance naturally through environmental selection. We need to have drugs that can combat these resistant strains. This topic focuses on the development and evaluation of lead compounds against *B. anthracis, Y. pestis*, and *F. tularensis* that are predicted to be efficacious against MDR strains of these pathogens.

In addition to the potential for exposure to emergent or engineered pathogens, currently identified pathogens naturally resistant to conventional antibiotics pose an equally serious threat. *B. pseudomallei*, the causative agent of melioidosis, is an emerging pathogen and a potential bioterrorism threat agent. *B pseudomallei* is categorized by the Centers for Disease Control and Prevention as a level B biological terrorism agent that must be handled under Biosafety Level 3 containment. *B. pseudomallei* is of particular concern due to the ease of acquiring strains from the environment, the ability to genetically manipulate the agent, lack of a melioidosis vaccine, and inherent resistance to many antibiotics. Furthermore, *B. pseudomallei* has been studied by several nations as a potential biological warfare agent, although it was never used. The mortality rate from *B. pseudomallei* varies depending on the type of infection, but in the case of disseminated septicemia can range from 50-90% when left untreated. Therefore, it is recommended that clinicians treat all melioidosis cases, even

in the case of mild disease, with intensive initial therapy of at least two weeks of intravenous (IV) antibiotics, followed by oral therapy for a minimum of three months. The standard therapy would be disastrous for military operations in the event of an attack. Given that *B. pseudomallei* is intrinsically resistant to many antibiotics including aminoglycosides, first- and second-generation cephalosporins, rifamycins and often quinolones and macrolides, new therapeutic options are needed. Therefore, this topic focuses on the discovery and development of drugs that are effective against *B. pseudomallei* infections.

Requirements:

This topic seeks proposals addressing the development of novel antimicrobial therapies for either *B. pseudomallei* and/or MDR strains of *B. anthracis*, *Y. pestis*, and *F. tularensis.* Proposals must focus on either or both:

1. Discovery and/or development of small molecule or peptide therapeutics for *B. pseudomallei.*
2. Discovery and/or development of small molecule or peptide therapeutics for MDR strains of *B. anthracis* and/or *Y. pestis* and/or *F. tularensis.*

Areas of particular focus include:

1. Evaluations of marketed drugs, investigational antimicrobial drugs undergoing clinical (Phase I/II/III) and preclinical compounds currently in development including repurposing existing drugs for other indications.
2. Discovery and /or development of novel antimicrobial therapies targeting 1) previously unexploited bacterial metabolic or physiological processes or 2) validated targets (i.e. targets that are currently exploited by approved antibiotics).
3. Discovery and/or development of therapeutic strategies to circumvent antimicrobial resistance mechanisms or potentiate the therapeutic efficacy of existing antibiotics (for example combination therapies).

Efforts will be prioritized as follows:

1. Broad-spectrum capability (in order of decreasing priority)
    a. Proposals focused on discovery and/or development of broad-spectrum antimicrobials effective against *B. pseudomallei* **and** MDR strains of *B. anthracis* **and** *F. tularensis* **and** *Y. pestis*.
    b. Proposals focused on discovery and/or development of antibiotics effective **only** against *B. pseudomallei.*
    c. Proposals focused on discovery and/or development of antibiotics effective against MDR strains of *B. anthracis* **and** *F. tularensis* **and** *Y. pestis.*
    d. Proposals focused on discovery and/or development of antibiotics individually effective against MDR strains of *B. anthracis* **or** *F. tularensis* **or** *Y. pestis.*
2. Preliminary data (in order of decreasing priority)
    a. Proposals with extensive preliminary data (MIC, preliminary *in vitro* ADME, proof-of-concept in *vivo* efficacy) for *B. pseduomallei* **and/or** pathogenic strains of *B. anthracis, Y. pestis, F. tularensis*, **with** predicted efficacy against MDR strains of *B. anthracis, F. tularensis* and *Y. pestis* will be given highest priority. Since access to collections of MDR BSL-3 biodefense pathogens are not currently available to the broad community, predicted efficacy for MDR

biodefense pathogens can be demonstrated using natural isolates of other pathogens with variable or high level resistance to specific antibiotics (i.e. Methicillin Resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumonia, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Escherichia coli*, etc.). However, these strains should only be used to assess a compound's ability to overcome resistance mechanisms by these MDR bacteria and effectively treat microbial growth, etc. Therefore efforts should not focus on development of antibiotics that are specific to these surrogate pathogens or their mechanisms of pathogenicity.

b. Proposals with limited preliminary data (MIC only) for *B. pseduomallei* **and/or** pathogenic strains of *B. anthracis, Y. pestis, F. tularensis*, **with** predicted efficacy against MDR strains of *B. anthracis, F. tularensis* and *Y. pestis.*

3. Stage of development (priority will be given to proposals that fulfill more advanced stages of development either previously, through work conducted in this proposal, or through conjunction of other complementary work outside this proposal)

a. Lead optimization - studies may include rational drug optimization using computational modeling and crystallography, *in vitro* MIC determination, studies of intracellular MIC (MIC for compounds with pathogen infected cell cultures), preliminary mechanism of action, *in vitro* ADME, etc.

b. Early preclinical - studies may include small animal studies including evaluation of pharmacokinetic (PK) parameters, safety, and efficacy.

c. Late preclinical/Candidate Selection – studies may include pilot PK and safety studies in non-human primates (NHP) leading to lead candidate selection for IND-enabling studies.

d. IND Enabling – studies may include completion of IND qualification studies and submission of IND resulting in progression to Phase I clinical trial (note: conducting the Phase I clinical trial is outside of the scope of this BAA).

The following is not of interest and considered outside scope of the topic:

1. Basic research studies focusing on host-pathogen interaction including target identification and/or validation or structural analysis of antibacterial targets.
2. Discovery and/or development of antibacterial therapies targeting the eukaryotic host cell as a therapeutic interdiction point.
3. Nucleic acid (i.e. siRNA, antisense) therapies.
4. Antibody-based therapies.
5. Protein-based therapies.
6. Phage-based therapies.
7. Early stage discovery efforts including high throughput assay development, construction of high throughput assay compound libraries, or preliminary high throughput assay screening to identify hit compounds.
8. Efforts focused solely on therapeutics for non-resistant strains of *B. anthracis, Y. pestis, F. tularensis.*
9. Clinical trials

APPENDIX C

ADVANCED AND EMERGING THREAT DIVISION

TOPIC AREA FUNDING OPPORTUNITIES

Thrust Two: Adaptive Medical Countermeasures and Technologies Biological Pretreatments

Objective: Defeat chemical and biological threats to the warfighter and nation through translational medicine (SHIELD and SUSTAIN mission capability and health)
To reach this goal, proposals that characterize and evaluate novel candidates against specified threat agents and address the topics presented below are desired. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks.

Topic: CBS-01
Alternate Manufacturing Processes for Recombinant Human Butyrylcholinesterase

DTRA is soliciting innovative research proposals in the area of recombinant butyrylcholinesterase (rBuChE) expression. Major limitations exist with plasma-derived hBuChE to include the large dose necessary for treatment, an anticipated overall cost per treatment dose of greater than $10,000 for plasma-derived hBuChE, issues with scalability and availability of human plamsa, and complexities associated with IV administration. These limitations necessitate an alternative platform capable of large scale production that is able to dramatically lower the cost/dose while still providing the same protection as plasma-derived BuChE. Human-like recombinant BuChE has been successfully expressed in alternative recombinant expression platforms, including transgenic goats, plants, insect cells, and cultured mammalian cells. However, due to the short half-life in circulation in the blood stream, challenges with furthering development exist which creates a potential operational problem of repeated dosing. The plasma derived hBuChE circulatory life of 10 days in humans has not been achieved by other recombinant forms. It is thought that this may be explained by the recombinant proteins lacking either the capability to produce tetrameric forms and/or the ability to be properly glycosylated and sialylated. These characteristics, however, do not appear to impact the enzymatic activity or OP binding capacity. Recent advances in protein chemistry with respect to tetramerization, sialylation, PEGylation and other stabilization strategies suggest that a more stable rBuChE product can be produced either with in situ modification of the enzyme during expression or via product modification after purification of the enzyme. However, a platform system that is capable of both rapid and large scale production of this enzyme with the required pharmacokinetic stability still needs to be developed.

DTRA is seeking approaches for development of recombinant human butyrylcholinesterase bioscavenger as a prophylactic countermeasure against OPs. Proteins must mimic the enzyme kinetic properties and in vivo pharmacokinetic profile of plasma-derived hBuChE when injected intramuscularly (I.M.) or intravenously (I.V.) into guinea pigs. Alternative routes of administration may be considered as long as the enzyme can be formulated and tested for I.M. and I.V. injection. Engineered forms of rBuChE may be considered, though a high level of homology to the parent human amino acid sequence is preferred. Strategies may include manipulation of protein expression machinery within the chosen organism or protein modifications and/or formulations post production. The methodology and rationale for down selection of potential bioscavenger candidates in vitro should be clearly stated.

Proposed research that primarily results in evolutionary improvements to the existing state of practice, that addresses only plant expression or bioscavenger pharamacokinetic stability (without addressing both components), or addresses bioscavengers other than BuChE will be considered non-responsive.
Metric: The produced protein must mimic the pharmacokinetics and organophosphorus nerve agent binding characteristics of human plasma-derived butyrylcholinesterase (hBuChE). The development of this capability is expected to result in a drug that can protect the warfighter from chemical threat agent exposures.

Thrust Two: Adaptive Medical Countermeasures and Technologies Biological Pretreatments

Objective: Defeat chemical and biological threats to the warfighter and nation through translational medicine (SHIELD and SUSTAIN mission capability and health)
To reach this goal, proposals that characterize and evaluate novel candidates against specified threat agents and address the topics presented below are desired. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposed efforts should be designed to have a 1 year base period and up to four option years, for a maximum of 5 years.

Topic: CBS-02
Pretreatments for Chemical Nerve Agent Exposure

This topic is for novel solutions for the pretreatment of nerve agent exposure. Development strategies may include, but are not limited to, high-throughput screening methods and rational design through novel computational or structural methods. Candidate compounds can include one of the following approaches:

1. Biologic candidates. These candidates include antibodies or enzymes that can neutralize nerve agents either through covalent sequestration or hydrolysis. Proposed solutions that merely bind in a non-covalent or non-hydrolyzing manner will not be considered responsive to this topic. Preference will be given to proposals that additionally address in vivo stability, potential immunogenicity, delivery and manufacturing scale/cost of the most promising candidates.
2. Small molecule candidates. Novel small molecules are sought that are capable of either (1) safely and effectively hydrolyzing and/or neutralizing nerve agents or (2) allosterically modulating acetylcholinesterase to promote protection against nerve agent. Proposals that address cholinesterase reactivators or their derivatives will not be considered responsive to this topic.

Metric: The mechanism of action of the candidate compounds must be established. Solutions must be effective against multiple nerve agents. Preference will be given to proposals that design solutions for V agents and their surrogates. If surrogates are used, the proposal must justify the choice of surrogate. In vitro, candidates must demonstrate fast ($k_{cat}/K_m > 1x10^7$ $M^{-1}min^{-1}$) and effective hydrolysis or covalent modification of nerve agent or surrogate to justify their continued development. In vivo, they must cause no adverse effects when administered and provide protection against 2-5xLD_{50} nerve agent or surrogate exposure for 10 days.

Adaptive Medical Countermeasures and Technologies Biological Pretreatments

Objective: Defeat chemical and biological threats to the warfighter and nation through translational medicine (SHIELD and SUSTAIN mission capability and health)

To reach this goal, proposals that characterize and evaluate novel candidates against specified threat agents and address the topics presented below are desired. In addition, innovative supportive technologies that can be

utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks.

Topic: CBS-03
Centrally Active Nerve Agent Treatment Systems (CANATs)

The currently fielded nerve agent treatment regimen has limited efficacy in the brain therefore it is unable to prevent the neuropathology and behavior deficits observed with nerve agent CNS-exposure. This topic seeks to fill this gap with the development of a novel reactivator that is capable of reactivating brain acetylcholinesterase. *Proposals that emphasize delivery of already developed oximes will not be considered. Proposals that focus on the reactivation of butrylcholinesterase will not be considered.*
Metric: Proposals should demonstrate the compound has a high probability of crossing the human blood-brain-barrier by demonstrating adequate membrane permeability and low P-glycoprotein efflux in established in vitro assays, as well as quantitation of unbound drug exposure in either animal brain tissue, cerebrospinal fluid or extracellular fluid when delivered by subcutaneous or oral administration. Experiments should also demonstrate reactivation of nerve agent, or an appropriate surrogate, inhibited acetylcholinesterase either *in vitro* or *in vivo*. *In vivo* work should not only demonstrate efficacy through reactivation of brain acetylcholinesterase but the neuroprotective value should be demonstrated with pathology and behavior tests. Successful proposals will emphasize the use of *in silico, in vitro,* and *in vivo* methods to demonstrate efficacy of the novel compound.

Enabling Science: Novel Threat Research

Objective: Provide necessary data to support development of countermeasures and tactics, techniques and procedures (TTPs) against technological surprise.

Topic: CBS-04
Resuspension Factors and Atmospheric Persistence of CB Particulate and Aerosol Threats.

This is a topic to determine the factors that govern CB particulate resuspension and half-life in the atmosphere. Resuspension factors are defined as the forces, interactions or characteristics that contribute to the removal of particles into the air after settling on surface. Persistence is defined as molecular and physical changes that effect survivability, transport and identification in the environment. Such knowledge may then be used to:

- Establish set baselines to assess resuspension risk as a function of specific characteristics of the particulate, the material and the environment
- Predict the transport of CB agent particulates from contaminated surfaces or sites
- Establish set baselines for half-life and information hazard management protocols
- Inform property characterization and factors required in modeling, simulation and prediction of agent half-life in the environment
- Estimate concentration of agent available for exposure in the atmosphere
- Estimate potential population doses.

Key questions and knowledge sought include but are not limited the following:

(1) Sensitivity analyses of factors that govern resuspension and/or persistence of CB agents.
   a. Understanding the relevant properties of the agents that regulate persistence including both molecular/physical and processing (e.g. diameter, agglomeration charge…)

b. Understanding the relevant properties of the environment that regulate persistence and/or resuspension (e.g. temperature, air quality, humidity, UV)
c. Identification of key transport particle processes and forces for both mechanical and environmental including but not limited to wind car traffic, human traffic, precipitation and washing
d. Understanding the role of deposition/ dissemination on resuspension or persistence.

(2) Linking laboratory studies on persistence and resuspension with real world information
a. Develop data correlation algorithms to link laboratory data with real world scenarios
i. Leveraging existing data
ii. Conduct a concise literature and data review of previous studies by other government, industrial, and academic institutions. Use of existing data will increase our return on investment by helping to focus study needs and will provide a body of data to form a comprehensive data set.
iii. Linking CB agents with environmental samples and real world examples (e.g. BtK, dust, pollen)

b. Validate correlation factors for DoD particulates of interest against actual environmental monitoring samples using relevant laboratory analyses
c. Validate laboratory studies in real world environments and scenarios
d. Development of adequate validated simulants for outdoor assessments of persistence and or resuspension

(3) Establishing relevant correlation factors to link DoD particulates of interest and environmental monitoring samples with the goal of both expanding understanding in the area of particulates and to validate small scale studies with agents to real world samples
a. Development of protocols that present a baseline from which other aerosol studies can be compared and assessed
b. Development of a standard set of laboratory conditions that inform policy makers and hazard assessment teams on the half-life of CB agents in the aerosol form
c. Development of rapid threat characterization tests to predict half-life and resuspension
d. Correlation/creation of aerosol and resuspension standards
i. Utilization of aerosol standard matrices including soil, grass, tarmac, terrestrial and aquatic ecosystems, etc.
ii. Utilization of other standard conditions including temperature ranges, UV levels, exposure times, wind speed, precipitation etc.

Proposals can be up to 3 years with the aim of identifying the key information that is most relevant to CB agent resuspension factors. This information will then be transitioned to other DoD and US Government programs responsible for determination of human exposure factors.

Metrics: Proposals will be judged according to scientific significance of the proposal as follows:
(1) The contribution the research makes to the approach, method, and understanding of the risk associated with CB agent resuspension.
(2) The soundness of the proposed methodology
(3) The adequacy and thoroughness of the theoretical background and best use of existing data/practices to determine resuspension factors
(4) The overall return on investment

(5) The viability of the proposed effort (can the specific steps and milestones be carried out with the indicated resources).

Data generated is required to be independently validated and proposals that to do not include this will be considered noncompliant.

Adaptive Medical Countermeasures, Novel Threat Research, Systems Biology, and Applied Math Tools

Objective: The application of systems biology, computational models and predictive toxicology methodologies can be utilized to characterize chemical threat agent toxicity at the molecular, cellular and organ-system level over time. Such a comprehensive predictive toxicology tool set will significantly decrease the number of animals needed for testing and the time for assessing chemical threat agent toxicity.

The ultimate goal of this effort is to develop a tool to predict the critical pathways perturbed by each toxicant and/or class of toxicants and link these pathways to adverse health outcomes, thus allowing for evaluation of human susceptibility and enabling understanding of the effects of exposure on individuals and populations.

Computational predictive toxicology tools can characterize chemical threats if the tools are sufficiently robust and have been validated with quality *in vitro* data. This topic is for proposals to develop and validate a predictive toxicology tool for multiple classes of advanced and emerging chemical threats including CWAs, TICs, TIMs, protein and peptide toxins, etc. This tool should include methodologies for data mining, structure activity relationships (i.e., QSAR) modeling, predictive perturbations of critical cellular and tissue responses, physiologically based pharmacokinetic (PBPK) modeling and extrapolation of experimental data (*in vitro, in vivo*, computational or any combination thereof) to the human system.

As part of the empirical data included in validating the predictive capabilities of the model, the proposal should include *in vitro* toxicity testing. These methods must identify and quantify key metabolic perturbations, as well as the resulting patterns and magnitudes of adverse effects that are predictive of adverse health outcomes. If the proposed effort includes *in vitro* assays, then it must be shown that the assays are already high-throughput or can be developed into high-throughput assays with meaningful output in supporting predictive toxicology tools. Tests should also address how specific biologic responses are affected by variations in the exposure scenario such as route, duration, and/or contaminants.

Proposed efforts should be designed to have a 1 year base period and up to four option years, for a maximum of up to 5 years, to fully develop and validate the predictive toxicology tool(s). Multi-disciplinary teams encompassing academia, industry and government laboratories are strongly encouraged.

Topic: CBS-05
Predictive Toxicology Tools for Enabling Rapid Countermeasure Development

All proposals, regardless of approach (*in vitro*, computational or some combination thereof) should include a section on experimental design that addresses determination of sample size and the statistical methods used to ensure power and robustness of results.

Metrics
All approaches should be aimed at the identification of primary mechanisms of action for early medical intervention to improve survival and quality of life following agent exposure. Characterization of the

mechanisms of action of advanced and emerging chemical threat agents should identify the cellular activities and perturbations at the molecular level to support medical countermeasures development. In addition to characterizing mechanisms of action, efforts should be made to identify biomarkers of exposure that can be measured/analyzed in an operationally relevant scenario prior to onset of symptoms to support early intervention.

In vitro Toxicity Approach - Develop analytical method(s) utilizing animal and/or human cell lines to establish predictive pathway-based toxicity for assessing the biological activity of advanced and emerging chemical threats utilizing cell morphology; phenotypic and functional characterization, such as cytotoxicity vs. cell line toxicity; metabolite analysis, proteome analysis, cell line biomarkers, and/or other toxic endpoints. Proposals will only be considered responsive if they consider a suite of assays that characterize traditional mechanisms of action (e.g. cholinesterase inhibition) as well as others beyond those associated with traditional agents. Such a comprehensive approach should lead to the identification of potential targets for prophylaxis or acutely administered therapeutics. Method(s) should be able to measure doses causing specific tissue perturbations (dose-response), as well as show early cellular changes leading to cell or organ injury. Methods should also determine the appropriate positive and negative controls that can be used to validate the assay results. The established methods and resulting data should be externally validated and be of sufficient quality to incorporate into the computational predictive toxicity tool. Proposals that do not address agents identified as an advanced and emerging chemical threat agents by DoD will not be considered responsive to this topic.

Predictive Toxicity Approach - The predictive toxicity tool should have a design that encompasses data mining (e.g. accessing, sorting, qualifying and prioritizing existing data, and electronic managing) using informed searches and informed algorithms for data interpretation and integration. The chemical characterization component of the tool should include a variety of empirical and computational methods, and compounds should be organized by classes. The tool should be capable of using advances in informatics, high-throughput /high-content screening technologies and systems biology to develop robust and flexible algorithms to screen advanced and emerging threats for acute toxicity. The tool should predict detailed mechanistic and dosimetry information; tissue distribution; perturbations of critical cellular responses (at molecular, cellular, and organ levels) and apply mathematical and advanced computer programs to help assess the hazard posed to individual humans, as well as populations. All predictive endpoints should be defined and tested using algorithms validated with empirical data. Third party external validation of the tools' predictive capabilities is required.

Thrusts of Enabling Science, Threat Activity Sensing and Reporting

Objective: ***Develop the capability to rapidly characterize CB threat properties and to predict CB threat behavior while interacting with physical and/or biological environments. (SENSE, SHAPE, SHIELD).***

Develop the capability to predict CB threat behavior while interacting with physical and/or biological environments. Accurate predictions depend on acquiring a fundamental understanding of physicochemical mechanisms (e.g., active and passive transport, reactivity) determining agent behavior.

To reach this goal, proposals are desired that result in development of ability to rapidly and quantitatively determine critical agent properties, together with enhanced understanding of fundamental physical, chemical, and biological mechanisms determining agent transport, reactivity, persistence, and availability in and on operationally relevant substrates, flora, or fauna. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks.

Topic: CBS-06
Methods for Rapid Prediction of Agent-Substrate Interactions Including Correlation of Chemical or Biological Agent Physical Properties to Determine Underlying Mechanisms

This topic is to determine agent agnostic mechanisms that can be used for predicting reactivity, fate and transport of a broad range of agents under a variety of environmental conditions or dissemination modalities. Proposals aimed at identification of critical properties of chemical and biological agents that can be linked to agent behavior and fate, on and within environmental or operational substrates, will be considered. Successful offerors will develop correlations between agent properties (e.g. hydrolysis rates and binding coefficients, vapor pressure, density, viscosity, etc.) and behavior (e.g. persistence (half-life)) or transport in the environment. The products from this effort are a critical first step in understanding and identifying the conditions and parameters that can be used for benchmarking agent fate and transport for use in predictive agent availability modeling for assessing risk. All methods and efforts should be tied to operational questions such as (a) what is it? (b) how bad is it? (c) how is it recognized? (d) what level of protection do current and developing countermeasures provide with respect to accomplishing military operations in a CB contaminated environment?
Successful offerings to this topic may include, but are not limited to, the following focus areas:

- Development and application of new combinatorial methods, to include physicochemical characterization, chemical synthesis, and data extraction algorithms, that permit rapid, systematic, and quantitative assessment of a broad range of variables influencing threat agent availability and hazard when present in operational environments.
- Establishment of agent baseline behavior that can serve as a standard for predicting agent behavior in other environments or environmental behavior in response to agents.
- Development and demonstration of improved modeling methods, rigorously validated by experiment, that forecast previously “unpredictable” rare events and effects due to extremes of environmental heterogeneity relevant to threat agent availability and hazard.
- Development of improved and validated correlations between (a) surface and subsurface availability of liquid and solid CB agent deposited on environmental substrates and (b) quantity and distribution of agent transferred to the skin or soldier ensemble under operational conditions.
- Novel methods for understanding CB agent interactions with indigenous cellular species of environmental flora, fauna and soil microbes, e.g. through utilization of advanced biocompatible platforms, locally controlled by an abiotic interface, that can induce and sense changes in cellular metabolism via chemical signatures.
- Modeling and testing of chemical or biological agent viability and substrate dispersion characteristics after a dissemination event (e.g. barrel bomb, IED, VED) for purposes of predictive risk modeling.
- Requirements and variables as follows:
    - Environmental variables to include, for example, substrate porosity, topology, and surface chemistry, temperature, humidity, and pH.
    - Availability parameters such as biological persistence, longevity, stability, quantitative binding constants, kinetic parameters, reaction products, permeation, surface availability, and

agent interactions with various surfaces and surface characteristics/properties should be considered.

- Predictive models will characterize mechanisms that determine agent interaction with substrates (e.g., adsorption, interstitial transport) (including interaction with additives or contaminants).
- Data and algorithms should allow for both rapid characterization of unknown chemical or biological agents, and improvement of existing agent fate models.
- Methods validated against lab and existing or new outdoor field studies.

Data validation should be informed by standard (e.g. ASTM) methods, and data and algorithms should be compatible with current and developing predictive models as well as applications suitable for handheld communication platforms.

Metrics:

1. Studies should characterize physiochemical properties of agent and mechanisms of agent persistence and transport under varying environmental conditions.
2. Establish predictive models/ algorithm correlations of agent behavior in the environment and in/on substrates and materials.
3. Based on agent data, establish agent agnostic predictive mechanisms.
4. Conduct independent validation studies to verify agent fate algorithm correlations by accounting for more than 90 percent of empirical agent persistence and availability
5. Validate algorithm using an unknown biological or chemical agent, - demonstrate the ability to quantify critical biological (e.g., genomics, virulence, transmissibility, longevity, stability and persistence) or physicochemical (e.g., vapor pressure, density, viscosity) properties within one month of receiving an unknown sample.

Topic: CBS-07
Interaction of Substrate-Mediated Transport and Catalyst Kinetics in Multicatalyst Systems

Background: Certain biological catalysts exhibit kinetics faster than the rate of substrate diffusion. This behavior has been variously attributed to, for example, (a) the ability of the catalyst scaffold to draw in and pre-orient substrate via dipolar electric fields or (b) for certain substrates (protons, electrons), quantum mechanical tunneling through the activation barrier to reaction. [1] It has also been suggested that the recently observed phenomenon of enzyme chemotaxis may play an underappreciated role in the activity of certain systems. [2] The ability of enzymes and scaffold components to respond to their environment by selectively directing mass transport is thought to play a fundamental role in the efficiency of biological catalytic cascades such as polymerases and many dehydrogenases. [3]

Scientists and engineers seeking to heterogenize homogeneous catalysts, for a wide variety of defense and industrial applications including those relevant to C-WMD, typically find a tradeoff between the desirable attributes of, on the one hand, the ability of the heterogeneous system to be compartmentalized and separated from the reaction mixture and, on the other hand, the more rapid rates of homogeneous catalysts. Mass transport limitations are thought to play a major role in diminishing the reactivity of heterogeneous catalysts, and today this is only partially mitigated by the use of highly porous scaffolds. [4] Strategies to introduce spatially anisotropic chemistry and topology into synthetic catalyst scaffolds have not been widely applied. However, the technology for tuning materials in this manner is increasingly refined, [5-7] and we believe that its convergence with the biological community will prove to be a fruitful pathway to both (a) better understand the role of substrate-mediated transport in biological multicatalyst systems and (b) develop the fundamental understanding needed to design disruptive materials for sensing, diagnostics, medical intervention, and

protection. The fabrication of model synthetic systems and re-engineered natural ones as tools in elucidating the role of substrate-mediated mass transport provides a focus to this convergence.

Impact: By means of accomplishing the objective articulated below, this research topic seeks to establish structure/property relationships that enable (a) design and tailoring of materials incorporating functionalities necessary for meeting DTRA C-WMD challenges; (b) understanding the response of natural and synthetic multicatalyst systems to relevant environmental variables; and (c) development of targeted effectors that alter the function of multicatalyst systems. Therefore, the knowledge generated as a result of conducting the research will be broadly applicable to core DTRA mission requirements for sensing and recognition, personnel protection, medical countermeasures, and treaty monitoring/verification. In addition, the research will support larger DoD goals for engineering of novel multifunctional materials to address a variety of critical mission needs. [8, 9]

Objective: Elucidate the role of substrate-mediated mass transport in the kinetics of multicatalyst systems by developing the predictive understanding required to couple new paradigms of directed molecular transport with the activity of supported catalysts.

The most competitive responses will, as tools to accomplishing this objective, develop and interrogate relevant multicatalyst model systems (here defined as heterogenous systems composed of two or more catalysts) or re-engineered natural systems that can: (1) rapidly separate components in a heterogeneous mixture, (2) selectively funnel individual components to and from specific catalytic centers, and (3) employ low-energy transport processes, ideally those relying only on ambient thermal energy and physicochemical interaction of the substrate with the scaffold and catalysts. Biotic, abiotic, or hybrid catalytic systems will be considered relevant to the goals of this research topic.

Competitive responses will likewise present a strategy that combines a theoretical approach, driven by a series of testable hypotheses, with material fabrication and evaluation; in particular, application of combinatorial design and computational learning algorithms is encouraged, as is modeling of substrate/scaffold/catalyst interactions, as framed within a careful design of experiments.

While the intent is to develop basic understanding, specific explored model systems must be shown to be relevant to countering the threat posed by weapons of mass destruction. For example, long-term relevance to one of the following could be established:

- Active and selective self-reporting catalytic systems for sensing and degradation of a nerve agent or biological toxin to innocuous products via e.g. oxidation or hydrolysis, where the threat molecule is present in a complex mixture of closely related synthesis byproducts and potential environmental foulants;
- Multicatalyst systems able to actively and selectively catalyze the binding and signal amplification of a toxicity biomarker, including those induced by exposure to chemical or biological agents, present in a complex biological fluid;
- Ability to mimic, sense and alter transport processes of biological catalytic cascades for diagnostic or therapeutic purposes directly relevant to C-WMD.

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APPENDIX D

PHYSICAL SCIENCE AND TECHNOLOGY DIVISION

TOPIC AREA FUNDING OPPORTUNITIES

Threat Activity Sensing and Reporting

Objective: Demonstrate a mobile sensing capability that utilizes a small, tactical unmanned autonomous platform that can be re-configured with integrated sensors for defined CB missions.

Technology Thrust: To develop the capability of CB sensors mounted on small unmanned platforms; a demonstration of a mobile platform equipped with CB sensors would be used in a series of specific operational scenarios that would test the potential of the technology. The mobile sensor would provide the user with a standoff method of detecting and identifying distant or obscured CB contaminated areas. The scenarios for the demonstration will include an urban environment and a base defense situation. Other scenarios may be developed with user input later.

Topic: CBT- 01
CB Mobile Sensing Technology Demonstration

Metric:
Mobile Platform: Demonstrate an existing small, tactical air vehicle capable of autonomous flight, flight time of over 30 minutes, with an integrated chemical or chemical/biological sensor, total payload not to exceed 1 pound, and ability to transmit sensor data back to the operator during flight, portable by one operator and hand launched/recovered, hover capability not required but preferred.
Sensor: Demonstrate an existing chemical sensor capable of detecting an open air simulant aerosol that can be integrated on a small unmanned air vehicle. The method of detection is open to current sensor or high TRL sensors. As part of the sensor design, it must be able to transmit real time data back to the operator. The capability of bio detection and sampling is not required but preferred. The platform does not have to carry both sensor types at the same time.

Threat Activity Sensing and Reporting

Objective: Using the architecture of chemical and/or biological sensors that have been integrated on a mobile platform, demonstrate a prototype capability that can rapidly replicate that design using a combination of basic components and a transportable additive manufacturing system.
Technology Thrust: The project revolves around the use of additive manufacturing technology to assemble at small unit level (battalion, ship, air base) an essentially disposable mobile sensing platform. This technology will allow isolated units to produce a mobile sensor to meet the needs of the unit in an as needed basis. The system will also be disposable so a heavily contaminated device can be destroyed and replaced. The primary task for this project is to evaluate the potential of additive manufacturing technology as a means of resupplying forces in the field.

Topic: CBT-02
Additive Manufacturing Fabrication of Mobile Chem/Bio Sensing Platforms

Metric:
Additive Manufacturing Technology: The additive manufacturing technology must be transportable by vehicle, suitable for field use by CBRNE teams, and capable of producing several devices within a short time period. The integrated sensor and platform mobile sensing system does not have to be fabricated completely within the additive manufacturing process; there can be pre-existing basic components that are further assembled by operators.
Mobile Sensing System: System consists of a simple platform that has the capability to move autonomously for 30 minutes. Both air and ground platforms are acceptable. The platform should be able to transmit real-time information back to the operator, which is preferred through electronic reporting but can also be by any indication that can be seen by the user at operating distance. The payload should consist of simple chemical and/or biological sensors, for example colorimetric film sensors or other methods to indicate presence of a threat.

Thrust Area 3: Threat Activity Sensing and Reporting

Objective: Demonstrate a rapid fabrication capability to quickly replenish expendable detection system components (for example: antibody-based assay tickets, DNA probes, or chemical colorimetric test kits).
Technology Thrust: The project would center on using rapid point-of-use fabrication methods to quickly replenish disposable (one-time use) detection kits. The technology could be used by small isolated units to produce necessary chemical and biological detection kits during an incident. The unit could have a small supply of detection kits on hand and then during an incident produce additional tickets if needed for a specific event.

Topic: CBT-03
Additive Manufacturing Replenishment of Expendable Chem/Bio Sensors

Metric:
Disposable Detection kit: Should be mature one-time use detection kit that has been tested against surrogate agents in a relevant environment. Must be able to be produced on the rapid fabrication system, some human assembly is allowed. The kit can be either a chemical or biological detection kit with limited refrigeration needs. The kit can be an expendable component of a larger detection/identification system, for example DNA assay probes.
Rapid Fabrication System: System must be transportable by a small or midsized vehicle, and operated using existing field unit power capabilities. The rapid manufacturing system should produce several detection tickets/probes per hour. System must include an analysis of solution impact upon current deployment practices (for example reduction in amount of storage space needed for detection tickets, reduction in logistical resupply, extension of detection system shelf life, fabrication system logistical burden, etc.)

Thrust Area 4: Rapid Response and Restoration S&T

Objective: ***Rapidly recover personnel and equipment to operational status (SUSTAIN and SHIELD)***

Products, technology, and capabilities that enhance coalition resiliency and military support to catastrophic civilian events, resulting in rapid and effective recovery and long term elimination of the threat.

To reach this goal, proposals that address the topics presented below are desired. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks. A lab demonstration employing chemical threats or their surrogates or precursors is desired, as is an assessment of scalability to field applications and related safety concerns/protocols/mitigation.

Topic: CBT-04
Enable rapid and active mitigation of the threat of bulk chemical weapon material, in the field

This topic solicits new capabilities for mitigation of the threat of chemical weapon material, contained in a barrel, munitions, or similar, non-dispersed form, with the assumption of a known storage location within a semi-permissive environment. Accomplishing the capability objectives below would allow for rapid elimination of the potential threat environment and restoration of normal military operations, ideally within a day or less.

- Capability Objective 1: Enable on-site treatment that results in chemical changes which eliminate the threat as a chemical weapon or weapon precursors. The outcome may be fully inert or may contain residuals that are not WMD materials but would be classified as a toxic industrial chemical to be left in place.
- Capability Objective 2: Enable on-site treatment that results in chemical changes which convert the chemical WMD material to a more benign state, facilitating safer transport of such WMD threats to subsequent areas for cooperative threat destruction.
- Capability Objective 3: Enhanced container exploitation tools that permit rapid ingress to the chemical WMD material or precursors.

In order to accomplish these capability objectives, innovative approaches are desired which might include but are not limited to the focus areas detailed below. Where applicable, offerors should also address the potential for broader relevance of their proposed innovations to other challenges (e.g. decontamination) in countering chemical or biological WMD.

- Microbes: identification and/or development of microbes that digest chemical weapon agents or precursors. This effort would pursue harvesting and/or modifying existing microbes (e.g. extremophiles) to enable digestion of chemical threats or their precursors in a sealed container, for rapid on-site remediation. An assessment is desired of existing microbes for applications to the broader mission space in countering chemical WMD, together with an investigation of synthetic biology and other techniques to adapt these microbes to the additional challenges of the elimination mission.
- Catalytic systems: deactivate chemical agents or their precursors through catalytic systems that reduce the activation energy for irreversible degradation or polymerization of the relevant chemical threats or their precursors, within a sealed container. It may be critical to enable enhanced intersection of the reactants with the catalytic sites in the absence of mechanical agitation, through active substrate-mediated transport. Exothermic reactions might be considered that produce “in situ” incineration—however, in all cases careful attention to process control and risk mitigation needs to be evident.
- Photochemistry: enable in-place elimination of chemical weapons or their precursors through application of systems, devices and materials to induce irreversible photo-degradation or photo-polymerization. In some cases, addition of photosensitizers may be required. This effort will

investigate whether materials or devices can induce rapid photo-conversion of the target chemical agent to a form that is unusable as a weapon. Approaches may include small, high power photonic sources, photosensitizing moieties, and others.

- Polymerization for transport: investigate the ability to introduce chemicals into the container which polymerize into an encapsulating material that renders the chemical inert or reduces the risk for transport. Approaches might include photo-polymerization, or chemically-induced polymerization, and might be used in conjunction with other methods to facilitate transport pre- or post-treatment.
- Barrel airlock delivery system. Rendering bulk chemical containers inert is envisioned to require initial access to the material and the ability to "drop in" items to start the chemical elimination process. This project will investigate innovative approaches to develop a container compatible "airlock" system for introducing chemical countermeasures and elimination processes to sealed barrels or munitions without the risk of potential exposure or environmental release.

APPENDIX E

DIAGNOSTICS, DETECTION AND DISEASE SURVEILLANCE DIVISION

TOPIC AREA FUNDING OPPORTUNITIES

Topic: CBA-01
Single Cell Biomarker Expression Methods/Analysis

Objective: Comprehensive proposals are sought for the development of point of need diagnostic platform technologies based on enhancement of methodologies for cell-based analysis of transcriptomic, regulatory and proteomic expression methods for verification and validation of biomarkers to human (and animal model) exposure to bio- and emerging-threat agents. An integrated approach is required in order to address confounding protein and gene expression patterns resultant from cell population (and sub-population) heterogeneity, as well as non-secreted and post-translationally modified forms of biomarkers. A teaming/collaborative proposal is encouraged.

Research areas of interest include comprehensively:

- Improved cell separation methods compatible with integration into hand-held form-factor medical device
- Miniaturization of optical/image analysis hardware and integration into hand-held form-factor medical device
- Development of methods enabling multiplex analyses of twelve (12) or more biomarkers simultaneously. Biomarker expression methods should be compatible with:
    - Protein expression
    - mRNA expression
    - miRNA (and other small RNAs) expression
- Improved detection sensitivity and specificity of in situ chemistries. This may be accomplished by (but not limited to):one or more of the following methods
    - in situ Signal amplification
    - in situ target amplification
    - Enhanced in situ binding kinetics
    - Enhanced cell permeability
    - Enhanced image analysis algorithms

Topic: CBA-02
Host-Based Biomarker/Assay Development

Objective: The CBA – Assays and Biomarkers Branch partners with a large variety of laboratories, each tasked to characterize threat agents and host response to threat agents using a variety of methods. The branch requests white papers from performers capable of accessing large, diverse datasets from a variety of sources and mining the data for optimal assay targets. Datasets may come in the form of threat genomes or chemical characteristics. A variety of host response data may include gene expression profiles (transcriptomic response), proteomic datasets, metabolomic datasets, or host physiological data. Host data may come from animal models or from de-identified human samples after natural exposure to an agent. Performers are NOT asked to propose the

generation of any new data, rather to integrate datasets from across the branches portfolio and mine the data for optimally informative assay targets. Performers are also NOT asked to develop any databases or data management systems, rather to access datasets through the division's existing data management platform.

Research areas of interest include:

- Assay target discovery for threat agents
- Molecular, immunological, or metabolic assay targets or assay signatures
- Threat agnostic approaches are highly encouraged as DTRA anticipates directing performer focus to the immediate needs of the Department of Defense
- Large, disparate data integration
- *In silico* validation of propose targets
- Open source data mining

Topic: CBA-03
Bioagent Infection of *In Vitro* Organ Models to Develop Companion Diagnostics

Objective: Comprehensive proposals are sought for the discovery of early-stage, human biomarkers of infection through biothreat agent infection studies including human clinical, animal models and three dimensional (3D) *in vitro* engineered organ models. It is expected that one viral and one bacterial agent will be chosen as model pathogens where human clinical cases are available and appropriate animal models have been verified. *In vitro* engineered organ models should focus on primary organs for pathogen entry and/or infection including but not limited to the lung-air interface, blood-brain-barrier, liver and gastro-intestinal interface. Focus for these organ models should be placed on engineering the 3D cellular microniche and include vascular and microvascular structures that would enable sustained viability for 8-12 week long infection studies. An integrated approach is required to address all phases of study culminating with *in situ* biomarker discovery during infection (with an emphasis on early-stage biomarkers), correlation of biomarker response in human, animal and engineered organ models, and iterative testing of therapeutic and/or vaccines using refined organ models. Ultimately, companion diagnostics will be developed and tested using the refined organ models. A teaming/collaborative proposal is encouraged. Proposals should address the following areas:

- Pathogen growth, exposure/infection of model system and analysis (one bacterial and one viral model)
- *In vitro,* 3D engineered organ models relevant to pathogen infection
- Appropriate animal models for bioagent infection and analysis
- Informatics (in situ biomarkers)
- Human infection/clinical cases and analysis
- Testing of medical countermeasures (MCM)
    - Determine success/failure of MCMs

        - Analyze how and why success/failure occurs

- Verification of companion diagnostics:

    - Test ability of biomarkers to predict efficacy of a specific drug/class for a targeted patient group based on accurate host response pathways

        - Compare drug effect (i.e., treatment vs control)

        - Differentiate responders from non-responders

    - Use organ models and human clinical studies to test ability of biomarkers to provide prognostic information indicative of disease aggressiveness

Topic: CBA-04
Next-generation analytic capabilities for BSV

Objective: Development of next-generation methodologies to enhance analytic capabilities in the detect-identify-respond timeline for a bioevent. Research should be exploratory, with low TRL, and should address long-term challenges in threat surveillance. Efforts should significantly contribute to the current body of knowledge and lead to new concepts for technology application that may have impact on future BSV analytic capabilities.

Topic: CBA-05
Biosurveillance Ecosystem (BSVE) Analytics 2.0

Objective: Ensure state of the art technologies are made rapidly accessible through the BSVE, this topic seeks to develop analytic applications (apps) to synthesize and interrogate multiple sources of data to provide high confidence in the prediction, early warning and forecasting (inclusive of mitigation strategies) of disease events. Metrics shall be devised such that successful utilization of these analytic tools will result in a measureable impact on the bioevent timeline. Efforts in this area should result in flexible, extensible, and sustainable analytics and models that are designed to plug into the BSVE as a la carte services rather than as standalone capabilities.

Research areas of interest include:

- Algorithms for rapid identification of: baseline deviation; novel/unknown pathogens, naturally-occurring versus intentional release

- Models to predict the likelihood of an outbreak, forecast the associated epi curves and impacts of interventions, and update forecast based on field (and simulated) data

- Applications to engage citizens via social media, crowdsourcing, gaming, etc.

Topic: CBA-06
Enhancing the Baseline

Objective: Advanced approaches for unique and emerging data collection, aggregation and provision of human, vector and animal/zoonotic health surveillance data. Data feeds should include traditional health surveillance sources as well as emerging feeds, such as: sequencing data, diagnostics, social media, news aggregators, etc. Efforts in this area should result in flexible, extensible, and sustainable data feeds that are designed to feed into JSTO products.

Research areas of interest include:

- Molecular Data
    - Fundamental knowledge of what genotype/phenotype data mean; viral evolution; species jump/outbreak prediction
    - Capability to model predicted phenotypes and potential for pathogen to become 'more' pathogenic, more transmissible, persistent, etc
- Human Social Cultural Behavioral data
- Environmental/climatological data
- Methods to integrate these baseline data to support disease prediction and early warning

APPENDIX F

TECHNOLOGY READINESS LEVEL (TRL) DEFINITIONS

INTRODUCTION

Technology Readiness Levels (TRLs) are a systematic metric/measurement system that supports assessments of the maturity of a particular technology and the consistent comparison of maturity between different types of technology. TRLs were originally developed and used by the National Aeronautics and Space Administration (NASA) for technology planning. The use of TRLs has been widely adopted in government and industry. The Department of Defense (DoD) has adopted the use of TRLs as documented in the current DoD-5000 series publications. The table below provides notional TRL descriptions for both non-medical and medical systems.

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
1. Basic principles observed and reported.	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.	**Review of Scientific Knowledge Base**. Active monitoring of scientific knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies.
2. Technology concept and/or application formulated.	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.	**Development of Hypotheses and Experimental Designs**. Scientific "paper studies" to generate research ideas, hypothesis, 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.

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
3. Analytical and experimental critical function and/or characteristic proof of concept.	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.	**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).

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
4. Component and/or breadboard validation[1] in laboratory environment.	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	**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) 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 armacodynamics 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).

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
5. Component and/or breadboard validation in relevant environment.	Fidelity of breadboard technology increases significantly. The basic technological components are integrated with reasonably realistic supporting elements so it can be tested in a simulated environment. Examples include "high fidelity" laboratory integration of components.	**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 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.

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
6. System/ subsystem model or prototype demonstration in a relevant environment.	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 simulated operational environment.	**GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s).** Manufacture GMP 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 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 animal 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 and pharmacokinetics assessment.

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
7. System prototype demonstration in an operational environment.	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 such as an aircraft, vehicle, or space. Examples include testing the prototype in a test bed aircraft.	**Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)[3].** Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate. Conduct Phase 2 clinical trial(s). *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[4]. 7B Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2)[3].

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
8. Actual system completed and qualified through test and demonstration.	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.	**Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials[3], 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 final 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.

Technology Readiness Level	Acquisition Guidebook (October 2012)	Medical Description (December 2008)
9. Actual system proven through successful mission operations.	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.	**Post-Licensure and Post-Approval Activities.** 9A Commence post-licensure/post-approval and Phase 4 study commitments, such as safety surveillance, data to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate[5]. 9B Maintain manufacturing capability as appropriate.

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

[2]This document does not serve as official FDA guidance. For the purposes of a regulatory application seeking licensure or approval for a specific medical product, additional data my be required by the FDA.

[3] Identification of later regulatory stages of clinical development in this documents (e.g. Phase 2, Phase 3) may not apply to some products being developed under the "Animal Rule." Other than human safety and pharmacology studies, no additional data may be feasible or ethical to obtain.

[4] These could include GLP animal efficacy studies required by the FDA at this stage in support of the Emergency Use Authorization (EUA). Requirements for issuance of an EUA will be handles on a case-by-case basis and will depend on the nature abd extent of the threat at any point during the product development timeline, from the initiation of Phase 1 studies through licusure or approval. GLP animal efficacy study requirements may also vay by product type (e.g. vaccine, therapeutic, prophylactic) and U.S. Government agency program office.

[5] For products approved under the "Animal Rule," confirmatory efficacy data is required and may be obtained from use during an event.

APPENDIX G

MANUFACTURING READINESS LEVELS (MRL)

The Government Accountability Office (GAO) has issued a Report to Congressional Committees titled "Best Practices: Stronger Practices Needed to Improve DoD Technology Transition Processes" (September 2006, GAO-06-883). The report can be accessed at: http://www.zyn.com/sbir/reference/GAO-d06883.pdf or obtain summary at: http://www.gao.gov/highlights/d06883high.pdf

In an attempt to address the concerns of the GAO, certain technology topics (Appendices A-C) state "MRL should be considered". For those topics, refer to the questions presented below. These questions do not need to be addressed in a proposal submission; they will be addressed during a project's period of performance to facilitate opportunities to better improve the potential for transitioning the technology development to an acquisition program.

Manufacturing Readiness Level Questions

- Has the technology reached a minimum Technology Readiness Level (TRL) 4 or higher? Refer to Appendix F for TRL definitions.

- If yes, give consideration to the following Manufacturing Readiness Level questions, where applicable:

  a. General
     - Is the technology reproducible?
     - If so, have the critical features and attributes been characterized using quantitative methods?
     - Are the performance and/or purity requirements measurable using standard laboratory methods?

  b. Technology and Industrial Base
     - Have manufacturing capabilities been anticipated/identified that are not readily available in the current industrial base?
     - Are any potential manufacturing shortfalls documented?
     - Are new materials, components, skills, and facilities anticipated?
     - If so, are any potential sources/resources identified and documented?
     - Have commercial potentials (e.g., spin-on, spin-off and dual-use) been considered?

  c. Materials
     - Have all concept materials been compared to EPA lists of hazardous materials?
     - Are any potential hazards identified and documented for the manufacture or use of the technology?

APPENDIX H

STATEMENT OF WORK FORMAT AND PREPARATION INSTRUCTIONS

Statement of Work Template

A Statement of Work must be included in Volume III, Supplemental Information, of the Phase II full proposal. The SOW does not have a page limit, but should be approximately 3-5 pages in length that is a separate and distinct document suitable for incorporation into the procurement instrument. Do not put proprietary data or restrictive markings in the SOW. Pages should be numbered and the initial page shall have a date (document date) shown under the title. Do not reference specific dates for the period of performance in the SOW.

The proposed SOW must accurately describe the work to be performed. The proposed SOW must also contain a summary description of the technical methodology as well as the task description, but not in so much detail as to make the SOW inflexible.

The SOW format follows:

(1) 1.0 - Objective: This section is intended to give a brief overview of the specialty area and should describe why the work is being pursued, and what you are trying to accomplish.

(2) 2.0 - Scope: This section includes a statement of what the SOW covers. This should include the technology area to be investigated, objectives/goals, and major milestones for the effort.

(3) 3.0 - Background: The Offeror must identify appropriate documents that are applicable to the effort to be performed. This section includes any information, explanations, or constraints that are necessary in order to understand the requirements. It may include relationship to previous, current and future operations. It may also include techniques previously tried and found ineffective.

(4) 4.0 - Tasks/Technical Requirements:

(a) This section contains the detailed description of tasks which represent the work to be performed that are contractually binding. Thus, this portion of SOW should be developed in an orderly progression and presented in sufficient detail to establish the feasibility of accomplishing the overall program goals. The work efforts should be segregated by performance year and by task(s)/sub-task(s) within each performance year Identify the performance year, task, sub-task using the decimal system (e.g. 4.1, 4.1.1, 4.1.1.1, 4.2, etc.). The sequence of performance must be presented the same as in Section III B of the technical proposal (refer to Attachment 4 of this BAA) and the SOW must contain every task to be accomplished to include a detailed performance schedule as required in Section IV of the technical proposal (refer to Attachment 4 of this BAA).

(b) The tasks must be definite, realistic, and clearly stated. Use “the contractor

shall" whenever the work statement expresses a provision that is binding. Use "should" or "may" whenever it is necessary to express a declaration of purpose. Use "will" in cases where no Offeror requirement is involved; e.g., power will be supplied by the Government. Use active voice in describing work to be performed.

(c) Do not use acronyms or abbreviations without spelling-out acronyms and abbreviations at the first use; place the abbreviation in parenthesis immediately following a spelled-out phrase.

(d) If presentations/meetings are identified in your schedule, include the following paragraph in your SOW:

> "Conduct presentations/meetings at times and places specified in the contract schedule."

APPENDIX I

Types of Research

Basic Research: Research that produces new knowledge in a scientific or technology area of interest and encompasses a broad, versus specific, area of application. Generally, basic research is research that does not have to transition to more advanced studies.

"Basic research is systematic study directed toward greater knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications towards processes or products in mind. It includes all scientific study and experimentation directed toward increasing fundamental knowledge and understanding in those fields of the physical, engineering, environmental, and life sciences related to long-term national security needs. It is farsighted high payoff research that provides the basis for technological progress. Basic research may lead to: (a) subsequent applied research and advanced technology developments in Defense-related technologies, and (b) new and improved military functional capabilities in areas such as communications, detection, tracking, surveillance, propulsion, mobility, guidance and control, navigation, energy conversion, materials and structures, and personnel support." (Defense Acquisition Guidebook, Oct 2012).

Applied Research: An expansion and application of knowledge to develop useful technologies to meet an identified need. Applied research may translate promising basic research into solutions for broadly defined military needs. This type of effort is typically inclusive of efforts that establish the initial feasibility and practicality of proposed solutions to technological challenges.

"Applied research is systematic study to understand the means to meet a recognized and specific need. It is a systematic expansion and application of knowledge to develop useful materials, devices, and systems or methods. It may be oriented, ultimately, toward the design, development, and improvement of prototypes and new processes to meet general mission area requirements. Applied research may translate promising basic research into solutions for broadly defined military needs, short of system development. This type of effort may vary from systematic mission-directed research beyond that in Budget Activity 1 to sophisticated breadboard hardware, study, programming and planning efforts that establish the initial feasibility and practicality of proposed solutions to technological challenges. It includes studies, investigations, and non-system specific technology efforts. The dominant characteristic is that applied research is directed toward general military needs with a view toward developing and evaluating the feasibility and practicality of proposed solutions and determining their parameters. Applied Research precedes system specific technology investigations or development. Program control of the Applied Research program element is normally exercised by general level of effort. Program elements in this category involve pre-Milestone B efforts, also known as Concept and Technology Development phase tasks, such as concept exploration efforts and paper studies of alternative concepts for meeting a mission need." (Defense Acquisition Guidebook, Oct 2012)

Advanced Technology Development: Research with direct relevance to identified military needs. Projects in this category should have the goal of moving out of science and technology

and into the acquisition process in the near term (though funding for subsequent development or procurement phases is not guaranteed).

"This budget activity includes development of subsystems and components and efforts to integrate subsystems and components into system prototypes for field experiments and/or tests in a simulated environment. Advanced Technology Development (ATD) includes concept and technology demonstrations of components and subsystems or system models. The models may be form, fit and function prototypes or scaled models that serve the same demonstration purpose. The results of this type of effort are proof of technological feasibility and assessment of subsystem and component operability and producibility rather than the development of hardware for service use. Projects in this category have a direct relevance to identified military needs. ATD demonstrates the general military utility or cost reduction potential of technology when applied to different types of military equipment or techniques. Program elements in this category involve pre-Milestone B efforts, such as system concept demonstration, joint and Service-specific experiments or Technology Demonstrations and generally have Technology Readiness Levels (TRL) of 4, 5, or 6. Projects in this category do not necessarily lead to subsequent development or procurement phases, but should have the goal of moving out of Science and Technology (S&T) and into the acquisition process within the future years defense program (FYDP). Upon successful completion of projects that have military utility, the technology should be available for transition." (Defense Acquisition Guidebook, Oct 2012)

For medical technology development, the strategy will convey an understanding of Food and Drug Administration (FDA) requirements for Investigational New Drug (IND) and New Drug Application (NDA) submissions. If a full proposal for an advanced technology development is invited, studies required to advance the technology from proof-of-concept through advanced animal studies in support of an FDA data package will be described in the full proposal submission and accompanied by a timeline. Full proposals will include a strategy for meeting Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Practice (GCP) requirements for product development as appropriate.

Advanced Component Development and Prototype: Efforts necessary to evaluate integrated technologies, representative modes or prototype systems in a high fidelity and realistic operating environment are funded in this budget activity. The Advanced Component Development and Prototype phase includes system specific efforts that help expedite technology transition from the laboratory to operational use. Emphasis is on proving component and subsystem maturity prior to integration in major and complex systems and may involve risk reduction initiatives. Program elements in this category involve efforts prior to Milestone B and are referred to as advanced component development activities and include technology demonstrations. Completion of Technology Readiness Levels 6 and 7 should be achieved for major programs. Program control is exercised at the program and project level. A logical progression of program phases and development and/or production funding must be evident in the FYDP." Source: FMR, Volume 2B, Chapter 5, page 5-5, paragraph E.