

Statement of Objectives (SOO)

for

Advanced Development and Manufacturing (ADM)

Capability for Medical Countermeasures (MCM)

(One Component of the Medical Countermeasures Initiative (MCMI))

I. Purpose

This contract will provide the Department of Defense (DoD) with the Advanced Development and Manufacturing (ADM) capability to rapidly develop, approve (through Food and Drug Administration (FDA) approval), and manufacture *Medical Countermeasures* (MCMs). The ADM Capability shall include a facility(ies), equipment and expertise (Contract Manufacturing Organization, Test and Evaluation, Contract Research Organization, and Fill/Finish).

II. Background

MCMs are needed to protect and treat military and civilian populations against chemical, biological, radiological, and nuclear attacks and outbreaks of naturally occurring *emerging*¹ and *genetically engineered infectious diseases*. The uncertainty of the threat, particularly bioterrorism or infectious diseases, requires new and adaptable approaches to respond faster and more effectively.

On December 29, 2010, the White House tasked the Secretary of Defense to:

1. Establish *agile* and *flexible* advanced development and manufacturing capabilities to support the development, licensure, and manufacturing of *medical countermeasures*;
2. Fund science and technology (S&T) efforts to develop the next generation of manufacturing systems and *regulatory science* technologies (that will enable the advanced development and manufacturing capability) and;
3. Establish a Medical Countermeasure Test and Evaluation Facility to provide state-of-the-art capacity and services to address the national demand for animal test and evaluation studies and related requirements for product development.

This contract responds to the task #1 above. DoD intends to provide a MCM pipeline of products that will support operations of the ADM capability. Consistent with its long-term goals, DoD envisions that this contract can produce an enduring capability to develop and manufacture MCM, based on the expected performance and efficiencies which will be evaluated during the course of the contract. The DoD anticipates issuing individual, competitive FAR based MCM contracts, whereby the ADM contractor will be the directed sub to develop and manufacture the product(s). Therefore the expected lifetime of the ADM will significantly exceed the period of performance of this contract. See Appendix I for the anticipated Government MCM pipeline.

III. Scope

The two (2) phases of this contract are identified below:

Phase 1: Months 1 through 24 – Establish, commission and validate (facility(ies) / equipment) for two (2) advanced development and manufacturing suites that use *agile, flexible (single use, disposable), modular and multi-product* technologies for MCM advanced development and manufacturing. Both suites must meet Biological Safety Level- 3 (BSL-3) standards. This contract will have up to three (3) options to incrementally increase the development and manufacturing capacity.

Phase 2: Months 25 through 120 – Support and maintain that capability in a state of readiness to support MCM development (under the animal rule as applicable) and manufacturing and assist in training personnel in its use. This includes transition and integration of new technologies, from pre-Investigational New Drug Application phase with readiness to support simultaneous operations, through FDA licensure.

¹ All *italicized* text refers to glossary terms.

The contractor's organizational structure shall include all required, facility(ies), equipment, and personnel to include business administration, professional/technical, certified Project Management Professionals (both for the infrastructure and products), *regulatory* expertise, and skilled labor (Contract Manufacturing Organization, Test and Evaluation, Contract Research Organization, and Fill/Finish) necessary to conduct advanced development and manufacturing of MCMs through FDA approval.

The contractor is required to be able to provide corporate sponsorship experience (from Investigational New Drug (IND) to FDA approval to include personnel and processes) in developing and gaining FDA approval of drugs.

The contractor shall participate in up to six (6) different Government led Integrated Product Teams (IPT) with representation by Government and contractor stakeholders. These IPTs will provide the government with full insight of operations, directly oversee the ADM operations, provide clear timely guidance, adjudicate conflicts and provide real-time feedback.

After Phase 1 is complete, the ADM capability shall be able to support the manufacture and release of ADM developed and FDA approved MCM within three (3) months of a Government request for the following maximum doses:

- Up to 1.5 million doses or 500,000 troop equivalent doses (TEDs)
- *Surge* up to 12 million doses which is equivalent to four (4)-million TEDs

NOTE: One (1) TED equates to three (3) doses.

During Phase 2, multi-disciplinary training to the Government and to other partners, including workshops, seminars, and training courses on best business practices, processes, and standing operating procedures, recent and emerging scientific technologies being used and/or developed in the ADM, associated laboratory and manufacturing quality assurance and control procedures, and laboratory skills needed to support applicable technician certifications for up to 15 industry and 25 government persons per year.

IV. Program Objectives

The overall goal for the contractor is to collaborate, and work with Government (to include the Food and Drug Administration) academia, and industry to reduce the overall time and cost associated with the development and manufacturing of Food and Drug Administration (FDA) approved MCMs. The ADM capability shall integrate *flexible, modular (single use, disposable), adaptable* and *scalable processes* and equipment that can provide:

- Capability that allows third parties to mature and provide products to the Government by leveraging ADM's core competencies and facilities while ensuring Intellectual Property is protected
- Streamlined advanced development capability that reduces risk (cost and schedule)
- Manufacturing *and warm-base* capabilities to rapidly respond to CBRN events and emerging and genetically engineered infectious diseases outbreaks by producing FDA approvable products or expand (*surge*) manufacturing of existing products without requiring additional regulatory approvals
- Strategies for using the ADM capability to support and facilitate transition of processes and technologies from Science and Technology - e.g., from Defense Advanced Research Projects Agency related work or the University Affiliated Research Center (UARC) associated with MCMI, currently under development. The type of requirements would include, but not limited to: Novel *platform/expression* systems for MCMs, Advancement in Regulatory Science, and advancements in *flexible manufacturing enabling technologies* for MCMs.
- Assistance and training in the areas of drug development and manufacturing including the use of the ADM capabilities

Commissioning shall be completed and documented by the contractor to ensure that all of the utilities and equipment (including water systems, clean steam, air handling, etc) have been installed properly and function according to specification.

Facility validation shall be completed and documented by the contractor to include:

- Installation qualification to ensure the equipment and utilities have been installed as per manufacturer specification
- Operational qualification to ensure that the equipment and utilities actually perform their specified functions at the required levels of performance
- Performance qualification to ensure that the utilities and equipment performs up to specification both under routine and stress conditions

Once the facility and equipment have been commissioned and validated, the ADM capability is expected to be ready to support transition and integration of new technologies from independent innovators, identify key needs for technology development, and conduct the development and manufacture of MCMs for the Government. This includes incorporating enabling science and technology (S&T) and novel platform and expression systems for delivery of products by leveraging technological and *regulatory science* advancements.

Milestones

Milestone 1: Within one (1) month of award the contractor shall submit to the Government for review and acceptance, an Integrated Master Plan (IMP). The IMP shall include the Work Breakdown Structure (WBS) and the Integrated Master Schedule (IMS) that correlate with the Contractor's Statement of Work (SOW). At a minimum with Level One (1) defined as the ADM Capability, both the fully loaded IMS and WBS must be defined to a minimum of five (5) levels throughout and shall be delineated to lower levels where appropriate to describe the work effort. The IMS shall also include all key regulatory and quality events, all contractual Milestone driven deliverables, and contractor-defined, project-specific elements in sufficient detail to outline the full scope of the effort required to establish, commission and validate the ADM capability. The IMP shall also include a detailed Major Equipment Purchase list that identifies the vendor(s), cost, and schedule for the purchase of all major equipment.

Milestone 2: Within three (3) months of award, the contractor shall provide the Government for review and acceptance a detailed Manufacturing Capability Plan describing the establishment, commissioning, and validation of a U.S.-based ADM capability.

- The Detailed Manufacturing Capability Plan shall include the following:
 - Site location(s), including site user requirement specifications, descriptions of site utilities and infrastructure, descriptions of local, state and federal permitting issues and security planning considerations;
 - Manufacturing capability regulatory compliance plan that addresses current Good Manufacturing Practices (cGMP) requirements, current Good Laboratory Practices (cGLP), current Good Clinical Practices (cGCP); in-process and product release analytical test method development and validation, applicable bio-safety standards; DoD security issues; Occupational Safety & Health Agency compliance and relevant USG/state/local Environmental Protection Agency requirements;

- Architectural/engineering drawings including manufacturing capability establishment, facilities layout, and mechanical layout and equipment requirements;
- Proposed manufacturing processes, including detailed descriptions of the flow of materials, personnel and equipment, upstream and downstream processing, formulation, filling and finishing/packaging unit operations, bulk and finished product acceptance specifications, overall capacity, and manufacturing support
- Description of the manufacturing capability quality assurance and regulatory acceptance including; quality systems, and regulatory milestones;
- Detailed milestones for commissioning and facility validation, including how these actions fit into the regulatory strategy;

Milestone 3: Within twelve (12) months of award, the contractor shall provide the Government for review and acceptance a Facility Operation Feasibility Plan for future development, manufacture, test, and release of final MCM products.

- The Facility Operation Feasibility Plan shall address the following key aspects:
 - Technology Transition
 - Preclinical;
 - Analytical methods development and test validation;
 - Clinical (including clinical supply manufacturing and adverse event tracking and reporting);
 - Regulatory;
 - Information Management Plan;
 - Program management;
 - Manufacturing management;
 - Site location(s) selection criteria;
 - Manufacturing/formulation;
 - Test and Evaluation
 - Fill/finish;
 - Quality Control and Assurance Program;
 - Stability Studies;
 - Storage and logistics;
 - Cost management and reporting;
 - Risk management and mitigation

Milestone 4: Complete facility validation of the ADM, within two (2) years of award and within one (1) month after completion of facility commissioning and validation the contractor shall submit for review and acceptance an equipment qualification/commissioning and facility validation summary with supporting documentation which includes, but is not limited to Installation Qualification, Operation Qualification, and Performance Qualification.

V. Place and Period of Performance

The ADM capability will be located in one or multiple locations within the United States and its territories and may include international participation. The contractor will establish, own and operate the MCM ADM capability within the United States. This project supports only the establishment and commissioning of the MCM ADM capability and the sustainment of the capability to enable the advanced development of vaccines, and/or drugs, and the rapid response to advanced development of vaccines, and/or drugs, and the rapid response to advanced development and manufacturing needs as they arise. All activities related to specific MCM advanced development and manufacturing requirements will be executed as separate contracts with third-party entities that will use this capability as a directed source.

This contract will be a ten- year effort, with a two (2) year base period for Phase 1, and four (4) two (2) year options for Phase 2.

VI. Parameters and Constraints

The Government anticipates future MCM contracts with third parties to use the ADM capability. Because the Government anticipates future contractors will utilize the MCM-ADM capability for MCM development and manufacturing, the ADM contractor will be a directed subcontractor of these third parties. The Government requires assurances that the ADM contractor will not use its economic leverage to obtain rights in the third party's subject inventions or technical data beyond those authorized by law in order to provide the needed service to the Government under its contract. For these reasons it is a requirement of the ADM contract that the Offeror provide a sharing plan, referred to as an Intellectual Property Management Plan, regarding all intellectual property that is generated under the ADM contract and/or that will be required to be practiced during the performance of the third party MCM contracts.

The Government recognizes that sharing plans may vary depending on the MCM product, the nature of the resources that will be shared, the allocation of rights in intellectual property made during or as a result of the use of the ADM capability, and plans for distributing the resources. The Offeror shall be required to submit a report concerning the sharing plan intended for each use of the ADM capability to develop or produce an MCM product. The report will be submitted within 30 days of the time of an award of the MCM third party contract and will outline how that product will be handled under the Intellectual Property Management Plan.

The requirement for a sharing plan does not alter any of the FAR or DFARS requirements between the Government and the ADM contractor. The rights in data and inventions with regard to the Government will be governed by the applicable clauses in the ADM contract. Sharing plans shall not include any terms that are prohibited by the applicable statutory and regulatory structure governing data rights and inventions.

Based on the above, the Offeror, as a requirement under this solicitation, shall describe its method for protecting third party intellectual property and the licensing arrangement it intends

to pursue regarding the intellectual property rights issues that may arise between the Offeror and third parties contracted by the Government.

The development and manufacturing of MCMs will be subject to regulation by the FDA as defined in the Code of Federal Regulations, Title 21 – Food and Drugs to include the “Animal Efficacy Rule.” This will be addressed in the specific Government contract for each individual MCM that will use the ADM capability.

The Code of Federal Regulations, Title 42 – Public Health, Part 73-Select Agents and Toxins applies. This also includes DoD biological surety requirements for personnel that have access to DoD-supplied Biological Select Agents and Toxins.

Appendix

Reference

Report titled: “Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government”, Defense Technical Information Center Accession Number: ADA506569, dated October 6, 2009.

Examples of DoD Medical Countermeasures Development Candidates

- Therapeutic
- Filovirus Vaccine (Alphavirus replicon particles)
- *Emerging Infectious Disease*, e.g., Flu - H1N1
- Broad Spectrum Antibacterial
- Trivalent Filovirus Vaccine (Alphavirus replicon particles)
- Tularemia Vaccine (Live Vaccine Strain)
- Ricin Vaccine (Recombinant)
- Tularemia Vaccine (Rationally Attenuated Mutant)
- Botulinum Vaccine (C,E,F) (Recombinant)
- Eastern Equine Encephalitis Vaccine (Alphavirus replicon particles)
- Staphylococcal Enterotoxin (B) Vaccine (Recombinant)

Glossary of Terms

<i>Advanced Development</i>	From 5 months prior to Investigational New Drug (IND)/Biological License Application to FDA approval
<i>Adaptable</i>	An ability to adjust advanced development and manufacturing processes in a timely and cost-efficient manner to adjust to the range of DoD product needs.
<i>Agile Manufacturing</i>	A combination of manufacturing technology, processes, tools, and training that are structured to enable prompt and timely changes in production line
<i>Disposable</i>	A single-use product designed to address a short-term need and intended to be disposed after its use. In the ADM context, this applies to technologies such as disposable bags for bioreactors that provide manufacturing flexibility and save cost and schedule by eliminating costly and time-consuming manufacturing equipment cleaning processes
<i>Emerging Infectious Diseases</i>	Infectious diseases that are caused by newly identified infectious agents. These may include diseases arising naturally due to evolutionary changes or genetically engineered pathogens.
<i>Enabling Technologies</i>	Technologies that can be used for optimization of product development, manufacturing, and/or regulatory science processes. Examples include, but are not limited to adequate and efficient expression systems that provide maximum yield; optimal upstream and downstream processes (e.g., time-efficient purification); disposable technologies to shorten the time that is required for cleaning validation between the manufacturing runs.
<i>Expression System</i>	A system that is specifically designed and constructed for the manufacturing of multiple copies of a desired protein. Expression technologies can be based on a variety of systems such as cellular or non-cellular.

<i>Flexible/flexible manufacturing</i>	Agile and adaptable manufacturing. See definitions above.
<i>Genetically engineered infectious diseases</i>	Infectious diseases that are caused by infectious agents resulting from direct manipulation of genetic material in order to alter the hereditary traits of a cell. Such diseases are essentially biological weapons created by terrorists or enemy nation states.
<i>Medical Countermeasures</i>	These are products that are created to prevent or treat human diseases whether they are caused by natural or human engineered pathogens.
<i>Modular</i>	Design based on standardized units or dimensions to enable efficient assembly or flexible arrangement and use for multiple purposes. Flexible manufacturing lines use various modules that represent discrete steps in the manufacturing process. Such discrete modules may or may not be needed for a given product manufacturing process and so can be added or removed as needed depending on the product being made. Such modularity supports flexible, adaptable and agile manufacturing approaches.
<i>Multi-product Capability</i>	A capability to manufacture multiple products in a single facility. This may be achieved by manufacturing different products in different production units and/or changing equipment within a production unit to manufacture different products over a period of time.
<i>Multi-product Surge</i>	The ability to significantly increase production (surge) of multiple medical countermeasures. This may be achieved in a parallel manner (different products being surged in different production units at the same time) and/or in a serial manner (different products surged in a production unit one after another using modular manufacturing methods to adjust to each successive product over time).
<i>No DoD Demand</i>	Lack of need for a product or production facilities by the DoD either at a given point in time or ever.
<i>Non-DoD Demand</i>	Need for production facilities by other than DoD entities. Non-DoD demand for ADM production capability is a potential source of revenue that could offset DoD cost of ownership by letting outside organizations pay for the use of the ADM when the DoD is not using it at full capacity.
<i>Platform Technology</i>	Standardized methods that can be used to significantly reduce the time and cost required to bring medical countermeasures to market. A classic example is the egg-based manufacturing method for seasonal influenza vaccine. The platform is the egg which is used to generate the immunogenic materials for each year's specific strain of flu.
<i>Regulatory Science</i>	Regulatory science is the assessment of the evaluation the safety, effectiveness, potency, quality and performance of FDA-regulated products. It is a modernization of US Food and Drug Administration (FDA) evaluation and approval processes to keep pace with technological innovations in medical product development. DoD will help advance regulatory science by

	collaborating with the on advancements made in medical technology associated with DoD medical programs
<i>Single Use</i>	A disposable manufacturing product designed to decrease costs and time associated with cleaning and maintaining manufacturing equipment (e.g., disposable bag for bioreactor). Single use products are typically used within a larger multiple use piece of equipment that houses the single use device and provides it processes providing such things as a controlled temperature environment, product stirring and/or agitation, etc.
<i>Surge Manufacturing</i>	Scale-up of the manufacturing process to meet temporary large-scale demand for a medical countermeasure, assuming that the product was developed, received FDA approval and ongoing production has been achieved. Surge may be met by running an existing process multiple times in parallel.
<i>Troop Equivalent Dose (TED)</i>	The number of doses that is required to provide protection or initial treatment course using a given countermeasure for a single person. For vaccines, a TED would be the number of immunizations needed to provide protection to a soldier.
<i>Validation</i>	Installation Qualification, Operational Qualification, and Performance Qualification of equipment and facility.
<i>Warm-Base</i>	The manufacturing capability needed to maintain product approval and produce quantities needed to meet DoD requirements for medical countermeasures. Factors impacting warm-base quantities may include, but are not limited to, FDA requirements for maintaining approval, shelf life, number of doses per TED, usage.