

Crossing the Valley of Death: Bringing Promising Medical Countermeasures to BioShield
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Testimony

Chairman Burr, Senator Kennedy and Members of the Committee:

I am honored to appear before your Committee. I am Colonel Joseph Palma, the Medical Director within the Office of the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense. I will provide information on Department of Defense efforts to develop promising new medical countermeasures to chemical, biological, radiological, and nuclear (CBRN) threats. I will also address concerns related to the transition of candidate technologies to the point where BioShield Act authorities can be used to fund the procurement. I will also share my thoughts on the perceived "Valley of Death" related to drug development. Following my comments, I welcome any questions the Committee may have and I will do my best to answer them.

DoD Chemical and Biological Defense Program — From Strategy to Programs

In accordance with Congressional authority, the Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs serves as focal point overseeing the Department's chemical and biological defense research, development, and acquisition. In preparation of the Fiscal Year 2006 President's Budget Submission for the Department's Chemical and Biological Defense Program, we used a new process based on the program reorganization that occurred in 2003. This improved process ensures that the Department's efforts in CBRN defense are closely aligned with strategic guidance and are driven by operational requirements, rather than being driven by technological approaches.

The planning process for the budget begins with the National Security Strategy, which establishes the position of the United States and outlines the defense strategy. Drawing from the direction and goals in NSS, the Joint Chiefs of Staff prepare and present the National Military Strategy. The National Military Strategy recommends military objectives and strategy, fiscally constrained force levels, and force options; and provides a risk assessment for programs.

A major aspect of the planning phase is the Joint Capabilities Development process. The Joint Capabilities Development approach to defense planning serves to focus attention on required capabilities while providing guidance to fit programs within the resources available and meet the defense goals. As stated in the guidance, a key Strategic Objective for the Department is to Secure the United States from Direct Attack—We will give top priority to dissuading, deterring, and defeating those who seek to harm the United States directly, including those extremist individuals or organizations that may possess and employ weapons of mass destruction.

The current CBRN Defense strategy emphasizes a capabilities-based approach rather than the previous approach, which provided greater emphasis on prioritizing threat agents and targeting budgetary resources based on validated intelligence. Capabilities-based

planning focuses more on how adversaries may challenge us than on whom those adversaries might be or where we might face them. It reduces the dependence on intelligence data and recognizes the impossibility of predicting complex events with precision. This strategy drives a top-down, competitive process that enables the Secretary to balance risk across the range of complex threats facing military personnel, to balance risk between current and future challenges, and to balance risk within fiscal constraints. I appreciate the Congress' support of the FY05 National Defense Authorization. I believe it is worth quoting from the congressional report language since the rationale coincides with the Department's approach:

The current law [10 USC 2370a] defines biological warfare threats primarily in intelligence terms. This is overly restrictive because intelligence on biological warfare threats is inherently limited due to the ease with which biological warfare programs can be concealed and dangerous pathogens and toxins can be acquired. The situation is further exacerbated by the rapid advancements in bio-technology that are widely available throughout the world. Additionally, the current law categorizes biological warfare agents by the time period in which they may become threats: near-, mid-, and far-term. For the same reasons that make it difficult to define biological warfare agents in terms of available intelligence, it is difficult to project the time periods during which such agents might become threats. In responding to such threats, more flexibility is needed in the medical components of the biological defense research program.

Key capabilities within the Chemical and Biological Defense Program are structured within the operational elements of Sense, Shape, Shield and Sustain.

- Sense includes advanced remote sensing, standoff detection and identification systems.
- Shape includes battlespace management, including modeling and simulation and the communication and decision systems to make appropriate responses and plans.
- Shield includes collective and individual protection and preventive medicines, such as vaccines.
- Sustain includes capabilities for decontamination and medical diagnostics and therapeutics.

This approach focuses on optimizing materiel solutions for CBRN defense by building a portfolio of capabilities that is robust and agile across the spectrum of requirements, including requirements to support homeland security.

Enhancing Countermeasures

As a supplement to the Joint Capabilities Development process, the Secretary of Defense provided direction to enhance the chemical and biological defense posture. The Joint Requirements Office for CBRN Defense and the Office of the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense led a comprehensive study that generated several options for increased investment based on the new requirements and accompanying risk. The study used an analytical methodology to define requirements for each Service and for the total Joint force.

Based on the study findings, senior leaders agreed to increase the investment for WMD countermeasures by \$2.1 billion in Fiscal Years 2006–2011. This increase includes \$800 million in military construction funding included in the Defense Health Program for a recapitalization of the facilities at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The increase also included \$1.3 billion for the Chemical and Biological Defense Program, bringing the total chemical and biological defense

investment to \$9.9 billion over that period. This investment strategy begins with the \$1.5 billion FY06 President's Budget Request. The Chemical and Biological Defense Program increase includes activities to enhance warfighter defense capabilities to include building a new test chamber for non-traditional agents; upgrading test and evaluation facilities; enhancing research and development efforts in areas of agent detection, early warning and battle management, decontamination, collective protection, and medical countermeasures.

The FY06 President's Budget Submission for the DoD Chemical and Biological Defense Program builds on the strategy and the existing capabilities fielded to protect U.S. forces against CBRN threats and includes the results of the study and biological warfare medical countermeasure initiatives. The Chemical and Biological Defense Program budget provides a balanced investment strategy that includes the procurement of capabilities to protect U.S. forces in the near-term (FY06), investment in advanced development to protect U.S. forces in the mid-term (FY07–11), and investment in the science and technology base to protect U.S. forces through the far term (FY12–19) and beyond. The two primary areas of increased emphasis in this year's budget are the CB Defense Program's test and evaluation infrastructure and novel biodefense initiatives.

This budget is based on technology needs and directions, restructured acquisition programs, and integrated Test & Evaluation (T&E) capabilities to execute these programs. The programs are time and funding sequenced to be executable in terms of having the technologies demonstrated and transitioned in synchronization with the T&E capabilities. Thus, the milestones of the acquisition programs are based on the availability of not only the financial resources, but the technology and T&E resources needed to execute the programs. The full effect of this integrated, executable program structure will begin to be realized in FY06.

Medical Countermeasures

In addition to the increase mentioned before, the FY06 President's Budget submission included an additional \$100 million for the CBDP to address biological warfare medical countermeasure initiatives. Of this funding, approximately 76% is applied to science and technology (S&T) efforts and approximately 24% is applied to advanced development efforts. These medical countermeasure initiatives will apply transformational approaches which leverage genomics, proteomics and systems biology data exploitation. The focus of these biodefense initiatives is on interrupting the disease cycle before and after exposure, as well as countering bioengineered threats.

The Chemical and Biological Defense Program has made progress in several areas of medical defense. I will briefly describe some recent successes. In 2003, the first successful application of the new "animal efficacy rule" occurred with Food & Drug Administration (FDA) approval of pyridostigmine bromide to increase survival after exposure to soman nerve agent poisoning. Evidence shows that administration of the drug before exposure to soman, together with atropine and pralidoxime given after exposure, increases survival. The FDA agreed that, based on the animal evidence of effectiveness, pyridostigmine bromide is likely to benefit humans exposed to soman. The safety of pyridostigmine bromide has been documented over years of clinical use in the treatment of the neuromuscular disease, myasthenia gravis.

In March 2005, a contract award was made for development of a chemical agent bioscavenger for a pre- or post-exposure treatment of nerve agent exposure. This

bioscavenger is being developed as a prophylactic regimen to protect the warfighter from incapacitation and death caused by organophosphorus nerve agents.

On the biological side, in early 2005, clinical trials began for a multivalent botulinum vaccine for serotypes A and B, and a plague vaccine; while in July, clinical trials will begin for Venezuelan Equine Encephalitis Vaccine.

Joint Vaccine Acquisition Program

The Joint Project Manager for Chemical Biological Medical Systems is responsible for systems acquisition, production, and deployment of FDA-approved medical countermeasures against chemical and biological agents for the Department of Defense, including the Joint Vaccine Acquisition Program (JVAP).

Near-term (FY06–07) biological medical countermeasure goals include transition to advanced development of bacterial (plague), and viral (Venezuelan Equine Encephalitis (VEE)) vaccines.

Mid-term (FY08–11) opportunities include advanced development of filovirus and ricin toxin vaccines, potential FDA approval of a reduced dosing schedule for the current anthrax vaccine) and a Botulinum A/B neurotoxin vaccine.

Long-term (FY12–20) targets include licensure of all near-term and mid-term vaccine candidates in advanced development to include Eastern and Western Equine Encephalitis (EEE and WEE) and combined filovirus vaccines. Furthermore, the program is investigating several alternatives to hypodermic needles for administration of vaccines, which will greatly reduce the medical logistics burden and cost associated with vaccination, and improve user compliance. Another thrust is to identify effective adjuvants to reduce the time and vaccine dose required for development of effective protective immunity. A strategic thrust is to develop innovative multi-agent vaccines that simultaneously target multiple pathogens through a single immunization series. This effort is supported by the investment the program is making in science and technology. Major technical challenges in the medical pretreatments capability area are being addressed both within the JVAP as well as in the science and technology base supporting the development and transition of vaccines and related medical countermeasures. These challenges include:

- defining appropriate in vitro and in vivo model systems for investigative purposes,
- determining mechanisms of action of the threat agents as well as their countermeasures,
- identifying appropriate immunogenic protective antigens for vaccine targets,
- stimulating immune responses to small molecules,
- selecting vector systems for recombinant protein vaccines,
- evaluating preliminary safety and efficacy data, determining dose and route of administration, and evaluating process-scale up potential. The development of acceptable surrogate markers of effectiveness is essential to obtain FDA licensure of medical CBD pretreatments, because challenging humans with chemical and biological threat agents to establish vaccine protective efficacy is unethical and prohibited.

Products currently licensed and procured under the JVAP are Anthrax Vaccine Adsorbed (AVA) and Vaccinia Immune Globulin IV, and Dryvax smallpox vaccine. More specifically, JVAP is developing the following vaccines for eventual FDA licensure, listed along with significant program milestones and events. The status of each follows:
- Plague vaccine: Phase 1 clinical trial is being conducted at the University of Kentucky, Lexington, KY. The Phase 1 clinical trial started on January 25, 2005.

- Recombinant Botulinum (rBOT) A/B vaccine: Phase 1 clinical trial is being conducted at the University of Kentucky, Lexington, KY. The Phase 1 clinical trial started on August 30, 2004.
- Venezuelan Equine Encephalitis (VEE) vaccine: A Phase 1 clinical trial will be conducted at Radiant Research, Austin, TX. The Phase 1 clinical trial is scheduled to start in July 2005.
- Vaccinia Immune Globulin Intravenous (VIG-IV): VIG-IV was licensed by the FDA. The FDA issued an approval letter to DVC on February 18, 2005 to market Vaccinia Immune Globulin Intravenous (human) (VIG-IV).

Interagency Program Coordination

The DoD Chemical and Biological Defense Program activities are informally coordinated with the Department of Health and Human Services, including the National Institute of Allergy and Infectious Diseases (NIAID), and the Centers for Disease and Control and Prevention. This coordination is evident by the DoD's active participation in the monthly DHHS Risk Management meetings for anthrax, smallpox, and botulinum toxin.

The DynPort Vaccine Company (DVC) is the DoD prime systems contractor for vaccine development. In addition to serving the needs of DoD, NIAID also funds DVC for some collaborative vaccine efforts. These awards included two grants to support the development of a vaccine candidate for botulinum toxin, a grant to support a Phase II trial of a Venezuelan Equine Encephalitis vaccine, and a contract to fund research on a vaccine candidate for tularemia.

It is important to note that some of the medical countermeasures currently being developed through CDC for the national stockpile have their technology basis in programs which originated in DoD. Examples are the next generation anthrax vaccine and cell culture derived smallpox vaccine. As such, DoD and CDC work cooperatively to leverage medical countermeasure programs of mutual interest including the role played by the DVC for such development. Both DoD and CDC have reviewed their programs to ensure there is no funding redundancy.

Management of the development and implementation of national security policies related to CBRN defense activities by multiple agencies of the U.S. Government are coordinated by the joint Homeland Security Council/National Security Council's Policy Coordination Committee for Biodefense. The DoD is represented on this Coordinating Committee.

Medical Countermeasures and Technology Transition – Bridging the “Valley of Death”

There are two rules of thumb that are based in some degree on the historical efforts with the pharmaceutical industry. First, fewer than one in one hundred candidate drugs will receive approval by the FDA for Investigational New Drug (IND) status, and of those, only about one in four will receive approval by the FDA. Second, once a product receives IND approval, it may take 8–10 years and \$500 – \$800 million or more to support the clinical trials and development manufacturing processes to bring a product to market. This does not include the research investment to develop candidate products.

The so-called “Valley Of Death” (VOD) is the time and investment gap between the identification of candidate medical products from the science and technology base and before they are ready for clinical trails.

We are looking at ways to speed up the overall development process for licensure of potential medical countermeasures, which can take 10-20 years. The most promising time

savings will probably occur in the initial 2-5 year period during the drug or vaccine candidate discovery phase and prior to the start of clinical trials, the so called VOD. With adequate funding, Good Manufacturing Practices (GMP) manufacturing capabilities, and required biocontainment facilities, the pre-clinical animal safety and toxicology testing might also be accelerated.

FDA has a “fast track” status for review of clinical trials data, but the required structure and time lines for clinical trials, and for product approval are not promising areas where significant shortening of the licensure process can occur.

The Department of Defense’s approach is a multi-pronged approach that includes a multi-disciplinary scientific and technical approach, potential changes or improvements in acquisition regulations, cooperative with industry and academia to facilitate venture investments, and continued investment in the medical countermeasures within the DoD Chemical and Biological Defense Program. Ultimately, some of the solution may lie outside the scope of the authorities of our Department and will require interagency cooperation.

BioShield Act

A critical aspect of interagency coordination is DoD support for Project BioShield. As Dr. Klein testified before the House Government Reform Committee in April 2003, it was the intention of the Department of Defense to support this effort. Our intentions have been put into action since that time. The first product that DoD may be able to transition to the Department of Health and Human Services (DHHS) under Project BioShield is the plasma derived bioscavenger. The DoD has awarded an initial contract through Phase I clinical trials, and upon completion, it may be eligible for procurement by the Department of Health and Human Services under Project BioShield.

It is important to note that military and civilian capabilities and concept of use for medical countermeasures do not always coincide. Military capabilities requirements generally focus on pre-exposure prophylaxis for a smaller, more defined population, while civilian requirements focus on post-exposure prophylaxis or treatment for a larger, more diverse population. The route of administration requirement for a product may be very different.

DoD’s role in Bioshield provides potential authorities and tools to streamline the acquisition of needed WMD medical countermeasures for the government. DoD’s role in Bioshield allows it to: a) leverage its military requirements for medical countermeasures with Department of Homeland Security and the Department of Health and Human Services resources for research, development, and procurement activities; b) continue to produce viable medical product candidates from the DoD research tech base; c) and maintain the unique DoD intramural medical biodefense program.

Thank you for the opportunity to address these issues. I will try to address any additional concerns or questions the Committee may have.