



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

AUG 10 2007

The Honorable Carl Levin
Chairman, Committee on Armed Services
United States Senate
Washington, DC 20510-6050

Dear Mr Chairman

The enclosed report responds to the request of the Department of Defense Appropriations Conference Report 109-676 The report requested that the Secretary of Defense provide the Congressional defense committees a report on medical countermeasures against acute radiation syndrome and similar threats

Attached is the final report that outlines a plan for procuring medical countermeasures to treat forward deployed service members against the lethal effects of acute radiation syndrome The report also identifies countermeasures required to protect service members against a nuclear or bioterrorist attack and provide a plan to forward deploy those countermeasures Lastly, the report provides an assessment of costs associated with implementing the plan

Thank you for your continued support of the Military Health System

Sincerely,

S. Ward Casscells, MD

Attachment
As stated

0 (7-3) (97 2111
14 (7-3) (173-1111)

cc
The Honorable John McCain
Ranking Member

RESP # 133324

**Department of Defense
Radiation Medical Countermeasures**



**A Report to Congress
on the identification, procurement, and deployment of
medical radiation countermeasures**



DoD RADIATION MEDICAL COUNTERMEASURES PLAN

OVERVIEW

The detonation of an improvised nuclear device (IND) has the potential to produce a large number of victims with a wide range of radiation-induced injuries. The extent of damage to forward deployed forces and local infrastructure depends on many factors. Additionally, contamination following a terrorist release of radionuclides from a radiological dispersal device (RDD) could result in a range of acute exposure doses as well as chronic exposure. Energy transfer from ionizing radiation to cells and tissues results in the formation of free radicals and reactive oxygen species along the path of the radiation. These molecules can induce potentially dangerous secondary changes in cells and tissues. Preparation and preplanning for optimal deployment and use of diagnostic tools and therapeutic agents along with the development of improved radiation medical countermeasures (RadCMs) are essential to limiting the morbidity and mortality from a mass casualty nuclear or radiation event.

The recently released Department of Defense (DoD) Chemical and Biological Defense Program (CBDP) Annual Report to Congress of April 2007 effectively highlights the DoD plan for developing, acquiring, and deploying chemical and biological medical countermeasures. Therefore, this Report to Congress will supplement the 2007 CBDP report and will expand on DoD plans for identifying, procuring, and forward deploying RadCMs that will treat service members against the lethal effects of acute radiation syndrome.

ACUTE RADIATION SYNDROME

Exposure to ionizing radiation induces injury to cells and tissue through a cascade of molecular and biochemical changes that lead to cell death or disruption depending on the dose. The Gray (Gy) is the unit used to measure the absorbed dose of any type of radiation, but it does not describe the biological effects of the different radiations.

Acute Radiation Syndrome (ARS) is the medical consequence of whole body exposure (or large proportion of the body) to a relatively large dose of radiation (above approximately 2 Gy) usually delivered from an external source over a period of seconds to days. The symptoms and progression of radiation injury occur even after the radiation exposure has ceased and there is a continuity of medical consequences from the ARS to the Delayed Effects of the Acute Radiation Exposure (DEARE) to chronic radiation damage. Progressive long-term tissue dysfunction may occur within weeks to months but may not manifest for years. Although radiation is a relatively weak carcinogen, significant human exposure to >1 Gy yields an increased lifetime risk of developing radiation-induced cancer.

ARS is a phased sequence of symptoms varying with individual radiation sensitivity, type of radiation, and the radiation absorbed dose. The extent of symptoms increases and the duration of each phase decreases with increasing absorbed radiation dose.

- Prodromal Phase Prodromal symptoms begin within hours of exposure and include nausea, vomiting, diarrhea, fatigue, weakness, fever, and headache. This is a nonspecific clinical response to acute radiation exposure. Early onset of symptoms in the absence of associated trauma suggests a large radiation exposure.

Radiogenic vomiting may easily be confused with psychogenic vomiting that often results from stress and realistic fear reactions. Use of oral prophylactic antiemetics (drugs effective against vomiting and nausea), such as granisetron (Kytrel®) and ondansetron (Zofran®), may be indicated in situations where high-dose radiation exposure is likely or unavoidable. The purpose of the drug would be to reduce other traumatic injuries after irradiation by maintaining short-term full physical capability. These medications will diminish the nausea and vomiting in a significant percentage of those personnel exposed and will consequently decrease the likelihood of injury in a compromised and temporarily debilitated individual. Prophylactic antiemetics do not change the degree of injury due to irradiation and are not radioprotectants.

Prodromal gastrointestinal symptoms generally do not last longer than 24 to 48 hours after exposure, but a vague weakness and fatigue can persist for an undetermined length of time. The time of onset, severity, and duration of these signs are dose dependent and dose-rate dependent. These signs can be used in conjunction with white blood cell differential counts to determine the presence and severity of the acute radiation syndrome. Unfortunately, prophylactic antiemetics diminish the reliability of nausea and emesis as indicators of radiation exposure.

- Latent Phase Following recovery from the prodromal phase, exposed individuals will be relatively symptom free for a period of time that varies with the dose. The latent phase is longest preceding bone-marrow depression of the "hematopoietic syndrome" (lowest absorbed dose) and may vary between 2 and 6 weeks. The latent phase is somewhat shorter prior to the "gastrointestinal syndrome" (intermediate absorbed dose), lasting from a few days to a week. It is shortest of all preceding the "neurovascular syndrome" (highest absorbed dose), lasting only a matter of hours. These times are exceedingly variable and may be modified by the presence of other disease or injury. Because of the extreme time variability, it is not practical to hospitalize all personnel suspected of having radiation injury early in the latent phase.

- Manifest Illness Phase This phase presents with clinical symptoms associated with the major organ system injured (marrow, intestinal, neurovascular) Both the rate and degree of decrease in blood cells are dose dependent Generally, if lymphocytes have decreased by 50 percent and are less than $1 \times 10^9/l$ [1000/ μl] within 24 to 48 hours, the patient has received at least a moderate dose of radiation In combined injuries, lymphocytes may be an unreliable indicator Patients with severe burns and/or trauma to more than one system often develop lymphopenia These injuries should be assessed by standard procedures, keeping in mind that the signs and symptoms of tissue injuries can mimic and obscure those caused by acute radiation effects

RADIATION MEDICAL COUNTERMEASURES

Medical management of radiation and combined injuries can be divided into three stages triage, emergency care, and definitive care During triage, patients are prioritized and rendered immediate lifesaving care Emergency care includes therapeutics and diagnostics necessary during the first 12 to 24 hours Definitive care is rendered when final disposition and therapeutic regimens are established

Therapeutic modalities will vary according to current medical knowledge and experience, the number of casualties, available medical facilities, and resources Recommendations for the treatment of a few casualties may not apply to the treatment of mass casualties because of limited resources A primary goal should be the evacuation of a radiation casualty prior to the onset of manifest illness

The amount of radiation received is greater when radioisotopes are inhaled and/or ingested than when they are absorbed through the skin Radiation exposure is associated with both acute and chronic effects, and treatment will vary with the specific radionuclide involved and the amount and route of exposure Consideration must be given to the target tissue(s) at greatest risk, cells of the hematopoietic system and gastrointestinal tract reproduce most rapidly and are the most sensitive to damage Regardless of the route of exposure, therapeutic intervention is time-sensitive and dependent on early recognition of an incident Importantly, a portfolio of therapeutic products will be required to successfully mitigate or treat the consequences of acute radiation exposure in a mass casualty scenario

Based largely on clinical experience with radiation therapy, it is now known that organs such as the lung, kidney, and liver are sensitive to injury following radiation exposure The mechanisms and extent of sub-clinical injury are not well understood Such "inapparent" injuries may result in organ system complications later in life For example, chronic renal failure has been observed in patients who have undergone radiation therapy, but the presumed damage to the renin-angiotensin system is not

understood. Similarly, pneumonitis and fibrosis are complications of radiation therapy. Immediate post-exposure intervention may minimize some of these complications.

RadCM requirements for mitigation and treatment of ARS are organ-system based for external radiation exposures and are isotope-specific for internalization through ingestion, inhalation or wound contamination. RadCM requirements for isotopes are primarily for a radiological dispersion device or nuclear accident and less so for an IND. Currently, the DoD Joint Deployed Formulary contains very few RadCMs for radiation exposures. General medical countermeasures used during a radiological event include

- **Antibiotics.** Includes anti-bacterial, anti-viral and anti-fungal agents to prevent and treat infections from burns, trauma and radiation-induced bone marrow suppression. Antibiotics will be forward deployed from pre-designated stockpiles close to the locality of the detonation for prophylactic treatment of trauma victims with survivability and initial treatment of neutropenic patients. Prevention and management of infection is the mainstay of therapy of medical casualties with moderate and severe radiation exposure and should include early measures to reduce pathogen acquisition, with emphasis on low-microbial-content food, acceptable water supplies, frequent hand washing (or wearing of gloves), and air filtration. During the neutropenic period, prophylactic use of selective gut decontamination with antibiotics that suppress aerobes but preserve anaerobes is recommended. The use of sucralfate or prostaglandin analogs may prevent gastric hemorrhage without decreasing gastric activity. When possible, early oral feeding is preferred to intravenous feeding to maintain the immunologic and physiologic integrity of the gut. Prevention and management of infection against gram-negative and gram-positive bacteria need be included only in institutions where these infections are prevalent. Antibiotic prophylaxis should be considered only in afebrile patients at the highest risk for infection. These patients have profound neutropenia that has an expected duration of more than 7 days. The degree of neutropenia (absolute neutrophil count [ANC] < 100/ μ l) is the greatest risk factor for developing infection. As the duration of neutropenia increases, the risk of secondary infections such as invasive mycoses also increases. For these reasons, adjuvant therapies such as the use of cytokines will prove invaluable in the treatment of the severely irradiated person. Radiation-induced damage of the gastrointestinal mucosa (destruction of crypt cells in the epithelial lining) can result in malabsorption, hemorrhage, and increased susceptibility to infection. Some patients can survive this type of injury despite the resulting excessive fluid loss and electrolyte imbalances, but their ability to control infections is severely compromised. Little data exist to define the antibiotics most useful in managing infections following radiation injury. In addition, new treatment options should be explored, including the use of probiotics.

- **Anti-emetics** prevent vomiting and relieve nausea induced from physical trauma or radiation exposure. Anti-emetics provide patient comfort and will be forward deployed from pre-designated stockpiles to the locality of the detonation for the treatment of vomiting and nausea in the comfort care of expectant and survivable patients.
- **Burn treatments.** Topical ointments and other medications will be in high demand for the treatment of burns. Burn treatments will be deployed in a rationed manner to the locality of the detonation for the immediate treatment of burn patients and to OCONUS/CONUS burn centers receiving patients from the locality of the event.
- **Pain control medications** such as morphine or other related agents provide patient comfort. Pain control medications will be deployed from pre-designated depots for this purpose to the locality of the blast for the management of patients.

Additional specific categories of radiation medical countermeasures are needed

- **Radioprotectants** help prevent injury from radiation-induced free radicals and other reactive species. Many such candidate drugs must be given before radiation exposure to achieve meaningful levels of protection. Radioprotectant drugs may also have a role following internal contamination to reduce the effects of ongoing exposure to ionizing radiation. Prophylactic agents also include compounds that are not directly cytoprotective, but enhance radiation tolerance of critical tissues, such agents might increase cellularity in target cell compartments or increase the expression of mediators that reduce the extent or severity of radiation injury.
 - **Scavenger drugs.** If radiation exposure is anticipated, a potential preventive strategy to limit the damage is pretreatment with "scavenger" drugs to eliminate the effects of free radicals and other reactive molecules.
 - **Amifostine (aminothiols)** represent one of several families of compounds that have been shown to be "radioprotective" when administered prior to radiation exposure. Amifostine has been licensed for use in cancer radiation therapy and chemotherapy when administered intravenously. Use of drugs such as amifostine as a pretreatment for radiation exposure will require more research to document safety and efficacy. Drugs that must be administered intravenously may be acceptable in the clinical setting but are not as practical in the battlefield or in a mass-casualty situation.
 - **5-androstenediol (5-AED)** is another promising radioprotective steroid compound. This androstene steroid is associated with low toxicity and long action and has been shown to enhance survival after exposure to 10.5 Gy of

radiation in the mouse model. Animal data for pre-radiation exposure have been published.

- **Neumune** (HE2100), a 5-AED radiation countermeasure, was being developed by Hollis-Eden Pharmaceuticals for the treatment of acute radiation syndrome. The clinical trials on rhesus monkeys were successful. According to a Hollis-Eden report, only 12.5% of the 40 Neumune-treated animals died versus 32.5% in the placebo group. Hollis-Eden had applied for a contract from the US Government under the BioShield Request for Proposals (RFP) for radiation countermeasures. After being encouraged for over two years that Neumune was in the competitive range, the RFP was canceled by Health and Human Services (HHS) in March 2007. According to HHS, "the product was no longer in the competitive range". Hollis-Eden has now withdrawn from the radiation countermeasure field and is no longer developing Neumune.
- **Nitroxides** are also effective radioprotectants that are currently in clinical trials to evaluate their anti-carcinogenic potential.
- **Cytokine (or growth factors) therapy for neutropenia** are administered for the mitigation and treatment of the blood cell-related symptoms of acute radiation syndrome including neutropenia (decrease in infection fighting white blood cells), thrombocytopenia (involved in blood clotting), and anemia (a decrease in red blood cells). After radiation damage of the hematopoietic system, growth factors and colony-stimulating factors that stimulate the production of lymphoid cells may aid in recovery and provide added protection against infection. Several pharmaceuticals are approved for use in patients who are either leukopenic or anemic as a consequence of cancer chemotherapy. Other promising compounds are in various stages of clinical evaluation.
 - Hematopoietic growth factors, such as filgrastim (Neupogen®), granulocyte colony-stimulating factor (G-CSF) and its pegylated form (Neulasta®), and sargramostim (Leukine®), a granulocyte-macrophage colony-stimulating factor (GM-CSF), are potent stimulators of hematopoiesis and shorten the time to recovery of neutrophils. The risk of infection and subsequent complications are directly related to depth and duration of neutropenia. Clinical support should be in the form of antibiotics and fresh, irradiated platelets and blood products. A marked reduction in infectious complications and reduced morbidity and mortality result from such clinical support used concurrently with filgrastim or sargramostim.

Cytokines will be deployed from pre-designated facilities to the locality of the detonation for the immediate protection and treatment of known or suspected radiation exposure with subsequent neutropenia

- Cytokines for neutropenia
 - G-CSF
 - Filgrastim (rHuG-CSF) [Neupogen® (Amgen)]
 - (Pegfilgrastim, PEGrHuG-CSF) [Neulasta® (Amgen)]
 - Lenograstim (rHuG-CSF) [Granocyte® (Chugai Pharmaceuticals)] not approved in USA
 - GM-CSF Sargramostim (rHuGM-CSF) [Leukine® (Berlex Labs)]
 - Cytokines for anemia Epoetin-alpha [Epogen® (Amgen)]
 - Cytokines for thrombocytopenia Interleukin 11 (IL-11) Oprelvakin (rIL-11) [Neumega® (Wyeth Labs)]
- Other possible radioprotectants that require further evaluation include anti-oxidants, nutraceutical drugs (e g , vitamin E analogs and soy isoflavone), and benzylsulfone analogs
- **Radiation mitigators** include agents that can eliminate radioactive material that has been incorporated into the body and thereby minimize internal radionuclide exposure, as well as agents that minimize the adverse health effects of radiation exposure, accelerate tissue recovery, or enhance repair processes Several radiation medical decontamination (removal) countermeasures are already FDA-approved, such as potassium iodide (KI) which blocks thyroid deposition of iodine radionucleotides and Prussian Blue (PB) which blocks absorption of cesium, rubidium, and thallium from the gastrointestinal tract and prevents recycling
 - **Potassium iodide** is a licensed drug (salt) that protects (blocks) the thyroid from radioactive iodine found in the plume and fallout from a nuclear detonation or radiological event or accident To be most effective, KI should be taken several hours before exposure or within 6 hours immediately after inhalation or ingestion of radioactive iodine for protective efficacy KI does not protect individuals from external radiation sources or from the effects of isotopes other than iodine KI is approved for oral administration following known or suspected exposure to radioactive iodide, and is particularly important for pregnant mothers, children, and young adults in the prevention of thyroid cancers KI needs to be deployed to the locality of the detonation and administered to those with known fallout or plume exposure first, and all others second

- Iostat® (Anbex), Thyrosafe® (RR Registrations), and Thyroshield® (Fleming) are approved for protection of the thyroid from uptake of radioactive iodine
- **Prussian Blue** [ferric hexacyanoferrate(II)] decorporates (removes) internalized radioactive cesium and thallium from the body. The pharmaceutical Prussian Blue (Radiogardase™, Heyl Chemi-Pharma) is approved by the FDA for the oral treatment of internal cesium or thallium contamination and has been used since the 1960s
 - Prussian Blue is currently stored at four US Army sites. US Army Medical Materiel Center Europe, Tripler Army Medical Center, Walter Reed Army Medical Center and Brooke Army Medical Center
 - Defense Health Program funding was used for this purchase
 - The Joint Staff will determine the allocation of PB across the Geographical Combatant Commands (GeoCOCOMs) for storage, management, and distribution to best fit the mission. GeoCOCOMs will develop an implementation plan for this radiotherapeutic within their area of responsibility
- Ion exchange resins such as sodium polystyrene sulfonate may be efficacious, but they have not been approved by the Food and Drug Administration. Aluminum hydroxide, which limits the uptake of strontium-90, must be given immediately after ingestion of this radioactive material because of its rapid absorption and incorporation into bone and tissues
- **Radiation therapeutics** given after overt symptoms develop to reduce pathophysiological radiation effects, facilitate tissue recovery or repair, or reverse fibrosis and other late effects
 - **Chelating agents** The internal contamination of victims may occur through inhalation, ingestion, and wound or burn contamination. Various factors, including the chemical form of the isotope and the pathway of absorption, may impact both the treatment method and effectiveness of radiocontaminant removal. When prevention of exposure has failed, treatment may include recapture of the radiocontaminant metals through binding with a chelator. Chelation involves the formation of stable ionic complexes which can be eliminated in urine, a process referred to as decorporation
 - DTPA (Ca-DTPA, Zn-DTPA diethylenetriaminepentaacetate) Hameln Pharmaceuticals. DTPA is approved by the FDA for the

chelation (decorporation or removal) of known or suspected internal contamination with the transuranium elements (plutonium, americium, or curium) DTPA is administered intravenously and has also been used for berkelium and californium DTPA is more effective in removing many of the heavy-metal, multivalent radionuclides The chelates are water soluble and excreted in urine DTPA metal complexes are not likely to release the radionuclide before excretion Repeated use of the calcium salt can deplete zinc and cause trace metal deficiencies

Ca-DTPA is recommended for the initial treatment because Ca-DTPA results in about a 10-fold higher rate of elimination of plutonium in the urine as compared to Zn-DTPA when given during the first 24 hours after exposure However 24 hours post exposure, Ca- and Zn-DTPA are equally effective at the elimination of radioactivity However Ca-DTPA is more toxic to the body than is Zn-DTPA, therefore, subsequent doses should consist of intravenous Zn-DTPA when possible Ca-DTPA may be continued if Zn-DTPA is not available, with concomitant mineral supplements containing zinc

If transuranic radioactive material is suspected, necessary DTPA products will be deployed to the locality of the detonation for the treatment of victims in the fallout and immediate vicinity of the blast with known or suspected internal contamination of radioactive material DTPA should not be used (per Center of Disease Control (CDC) guidelines) if the radioactive material is either uranium or neptunium This policy is consistent with that of the U S Strategic National Stockpile (SNS) Distribution Program and provides significant protection for U S personnel against the use of radioactive transuranics (plutonium, americium, curium) as terrorist weapons

- Dimercaprol forms stable chelates with mercury, lead, arsenic, gold, bismuth, chromium, and nickel and therefore may be considered for the treatment of internal contamination with the radioisotopes of these elements Penicillamine chelates copper, iron, mercury, lead, gold, and possibly other heavy metals
- Mobilizing agents are most effective if they are administered soon after the exposure to the isotope and may reduce the thyroid's retention of radioiodine Increasing oral fluids increases tritium excretion

- Propylthiouracil
- Methimazole

IDENTIFICATION OF RADIATION MEDICAL COUNTERMEASURES

DOD Chemical And Biological Defense Program:

Assistant to the Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs [ATSD (NCB)] In accordance with 50 USC 1522, the ATSD (NCB) provides oversight of the CBDP science and technology (S&T) base programs and serves as the single office within the Office of the Secretary of Defense for research, development, and acquisition (RDA) of the DoD CBDP, including interagency and international coordination efforts. The USD(AT&L) serves as the Defense Acquisition Executive (DAE) and Milestone Decision Authority (MDA) for the DoD CBDP. The Under Secretary of Defense (Acquisitions Technology & Logistics) delegates Milestone Decision Authority to the Army Acquisition Executive (AAE), who has further delegated MDA responsibility to the Joint Program Executive Officer for Chemical and Biological Defense (JPEO-CBD). This structure maintains a vertically integrated chain-of-command.

While the public law specifically addresses only chemical-biological (CB) defense RDA activities, DoD CBDP planning includes radiological and nuclear defense along with CB defense in its development and procurement activities. However, radiological and nuclear defense capabilities within the CBDP are limited to certain types of radiation detection equipment, modeling and simulation capabilities, and medical research on radioprotectants. Various other radiological and nuclear defense efforts, including systems for nuclear and radiation hardening, nuclear detection, medical radiological defense, and other selected programs are outside the scope of the CBDP.

Joint Requirements Office for Chemical, Biological, Radiological, and Nuclear (JRO-CBRN) Defense (JRO-CBRN). The DoD JRO-CBRN Defense coordinates all medical NCB defense requirements. It is the single office within DoD under the Chairman of the Joint Chiefs of Staff responsible for planning, coordination, and approval of joint CBRN defense operational requirements and serving as the focal point for Service, combatant command, and Joint Staff requirements generation. They coordinate with the Services and Combatant Commanders to develop joint CBRN requirements, an overarching CBRN defense architecture and a joint capabilities roadmap for coordinating and integrating CBRN defense operational capabilities for material and non-material solutions.

Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD). The JPEO-CBD is the principal advocate and single point of contact for all CBRN detection, vaccine and medical diagnostic development and acquisition efforts and

supports advanced research, development, acquisition and fielding of CBRN medical countermeasures. JPEO-CBD makes initial acquisition of radiation countermeasures, sustainment acquisition is managed by the Defense Logistics Agency (DLA) and supporting medical logistic agencies of each Service.

The JPEO-CBD reports to the AAE and serves as the CBDP Material Developer and oversees Life Cycle Acquisition Management for assigned system acquisition programs within the CBDP. The JPEO provides intensive centralized management of assigned medical and non-medical programs to expedite material solutions for validated CBRN deficiencies. The JPEO-CBD monitors technology based activities to promote and facilitate transfer and acceleration of emerging technologies to user applications across the military services.

The JPEO supports all military services to include homeland defense, allies, and U.S. citizens and troops abroad. The JPEO-CBD establishes and sustains responsive life cycle management, implements acquisition reform, focusing on the use of best practices, maximizes knowledge, technology, and industrial bases by partnering with government, academic, and commercial organizations to achieve optimal capabilities, enhances user satisfaction to retain and expand its user base, and maximizes employee potential.

Joint Project Manager Chemical Biological Medical Systems (JPEO-CBD/ JPM-CBMS). The JPM-CBMS is responsible for developing, procuring, fielding, and sustaining medical protection and treatment capabilities against CBRN agents. All products are submitted through the FDA licensing or approval processes. The JPM-CBMS Office is comprised of a headquarters and support element and two Joint Product Management Offices: the Joint Vaccine Acquisition Program (JVAP) and the Medical Identification and Treatment Systems (MITS).

There are at least one hundred drugs currently being investigated as potential radiation countermeasures but few of these have reached the stage of advanced research and development. Advances and results produced by science and technology don't go directly to the warfighter. When a promising RadCM is ready for advanced development, the JPEO-CBD/ JPM-CBMS funds advanced research. If a RadCM technology becomes technologically mature and FDA approved, the JPM-CBMS will fund initial capability procurement for the Services and then subsequently transfer contracts to DLA for sustainment procurement by individual Services. Logistics is a critical component in the JPM-CBMS strategic plan to provide RadCMs and alternative procurement strategies are actively being explored to reduce costs to the Services.

Joint Product Manager, Medical Identification and Treatment Systems (JPEO-CBD / JPM CBMS-MITS). The JPM-CBMS MITS centrally manages the development, acquisition and fielding of products used for the prophylaxis, treatment and diagnosis of chemical, biological and radiation agent exposure in U.S. Service.

members. The JPM CBMS-MITS anticipates releasing a performance-based RFP for the advanced development of radiation medical countermeasures in the summer 2007 with a contract award anticipated shortly afterwards. A Sources Sought Notice was released April 2007 to identify additional industry interest in developing a safe and effective medical countermeasure against radiation injury.

Defense Threat Reduction Agency Joint Science and Technology Office (DTRA-JSTO). The DTRA-JSTO manages and integrates all DoD CBDP medical (and physical) chemical, biological, and radiological science and technology efforts. The JSTO addresses DoD-wide requirements developed by the Joint Requirements Office (JRO-CBRND). JSTO ranks potential projects based on technical and programmatic perspectives based on two questions: Is it sound science? Does it meet the needs articulated by the JRO and JPEO? They solicit the service laboratories, industry, academia, the Department of Energy (DoE) national laboratories and federally funded research and development centers. The best responses from these queries result in JSTO funding basic medical countermeasure research.

The JRO-CBRN partners with Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) and the Defense Threat Reduction Agency (DTRA) Science and Technology Office (JSTO). JRO-CBRN leads the development of the DoD CBDP POM with JPEO-CBD, JSTO-CBD, and CBDP T&E Executive support. The JRO doesn't set quantities of medical countermeasures to be produced, that decision is based on current validated threats.

Armed Forces Radiobiology Research Institute (AFRRI). AFRRI is the primary DoD repository of medical radiological defense expertise in the DoD and is funded through the Defense Health Program, which is overseen by the Assistant Secretary of Defense for Health Affairs [ASD(HA)] through the Uniformed Services University for the Health Sciences. A comprehensive strategy and program for medical radiological defense is under development by ASD(HA). While AFRRI's research efforts may support the requirements of the warfighter as developed by the JRO-CBRND, AFRRI programmatic funding is separate from the DoD CBDP.

Each of the Military Departments—Army, Air Force, and Navy, including the Marine Corps—plan and execute CBRN defense programs, from basic research through procurement and sustainment via the DOD CBDP. In fulfilling their responsibilities, the military departments ensure coordination and integration with other CBRN defense organizations. The Military Departments play critical roles in the execution of all phases of CBRN research, development, and acquisition and provide the essential infrastructure, which includes personnel with unique scientific, technical, and management expertise, and the laboratory and test facilities to meet the demands of developing and fielding CBRN defense equipment.

Interagency Coordination

The overall DoD budgetary support for medical countermeasures to address radiation and nuclear threats is relatively modest compared with that allocated to biodefense and these support levels are not expected to significantly increase. Given these constrained resources, and the potentially broad spectrum of needs, interagency cooperation is essential to most effectively leverage resources and to repair critical infrastructure.

Several organizations within the U.S. government are developing CBRN defense technologies. Five organizations with which the CBDP currently has formal coordination efforts include (1) Defense Advanced Research Projects Agency (DARPA), (2) the Counterproliferation Program Review Committee (CPRC), (3) Technical Support Working Group (TSWG), (4) the Department of Homeland Security (DHS) Science and Technology Directorate, and (5) HHS.

The DoD-CBDP actively coordinates with the HHS, Office of the Biomedical Advance Research and Development Authority (HHS/OS/ASPR/BARDA), National Institutes of Health, National Institute of Allergy and Infectious Diseases [NIAID], Food and Drug Administration [FDA], Centers for Disease Control and Prevention [CDC] and other federal agencies on issues relating to all medical countermeasures research, development, acquisition and use, including radiological and nuclear countermeasures.

Department of Health and Human Services

To encourage the development of new medical countermeasures against CBRN agents to treat the citizens of the United States, and to speed the delivery and use of new medical countermeasures in the time of an attack, President George W. Bush proposed, and Congress subsequently enacted, the Project BioShield Act of 2004. Project BioShield provides incentives and funding mechanisms to develop and make available drugs and vaccines to protect against CBRN attack. Project BioShield created several mechanisms to help the HHS (and DoD) address gaps in the medical countermeasures development pipeline, including broadening the commercial industrial base capability. These mechanisms include:

- Ensuring resources are available to HHS to pay for next-generation medical countermeasures
- Expediting the conduct of National Institutes of Health (NIH) research and development on medical countermeasures based on the most promising recent scientific discoveries
- Giving the FDA the ability to make promising treatments quickly available in emergency situations

Under Project BioShield, HHS can encourage companies to partner with the government, and if they meet milestones and develop a licensable countermeasure, assure industry there will be money available to them for the purchase of that product. This relies on the ability of the Federal government to define its requirements accurately and assure that funds will be available to purchase critical countermeasures, regardless of the level of appropriations for the year in question.

The HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE, now BARDA) Strategy and Implementation Plan for (CBRN) Threats (the PHEMCE Strategy) establishes the principles and processes for identifying priority threat areas and requirements for medical countermeasure development and acquisition, including those medical countermeasures to be developed or acquired under the authorities of the Project BioShield Act of 2004.

HHS issued a Sources Sought Notice (SSN) on May 31, 2007 to conduct market research in accordance with Federal Acquisition Regulation, Part 10 to identify potential sources and gather information on current capabilities within the market for providing medical countermeasures for neutropenia arising as a consequence of acute radiation syndrome (ARS). HHS anticipates pursuing the initial acquisition of one hundred thousand (100,000) treatment courses of the ARS medical countermeasure. It is anticipated the product will be licensed/approved for ARS use by the FDA and will be stable for at least 24 months. There will be options for up to an additional one hundred thousand (100,000) treatment courses to meet the USG requirement of at least 200,000 treatment courses. It is anticipated HHS will announce a RFP in August 2007, with proposals due in November 2007 for a product to treat ARS-induced neutropenia in a declared emergency under Emergency Use Authorization (EUA).

The National Defense Authorization Act of 2004 (P.L. 108-136) includes provisions on how DoD interacts with and supports HHS with respect to BioShield, a critical aspect of interagency coordination. DoD's role in BioShield allows it to leverage HHS resources for research, development, and procurement activities to achieve DoD requirements for medical countermeasures, particularly when HHS and DoD requirements overlap. The DoD BioShield provisions allow the ability to contract for procurement up to five years in advance of product availability, increase simple acquisition thresholds, and allow DoD to provide funds to HHS to support BioShield efforts. This latter provision allows DoD to leverage the more flexible BioShield Act acquisition requirements available to HHS. Consequently, HHS likely will focus on developing RadCM for the hematopoietic syndrome while DOD will concentrate on RadCM for the gastrointestinal syndrome.

HHS has assigned the NIH the responsibility to identify, characterize, and develop new medical countermeasures against radiological or nuclear attacks. The National Institute of Allergy and Infectious Diseases (NIH/NIAID) conducts and supports research

on allergic and immunologic diseases and disorders and infectious diseases, including research on and development of countermeasures to agents of bioterrorism and radiation exposures. NIAID has funded numerous projects including ARS medical countermeasure screening programs in cell-based and rodent models at multiple institutions around the country, development of three Good Laboratory Practices animal testing facilities to evaluate the efficacy of medical countermeasures against ARS, eight Centers for Medical Countermeasures against Radiation at academic institutions around the country, and intramural research programs at the DOD AFRRRI and the National Cancer Institute

NIAID has used Project BioShield authorities to award grants and contracts for research leading to medical countermeasures against radiological or nuclear terrorist attacks, including the development of improved diethylenetriaminepentaacetate (DTPA) for radionuclide chelation. These contracts will support the discovery and demonstration of proof-of-concept of prodrugs or alternative (oral, inhalation, or transdermal) formulations of DTPA that deliver plasma levels sufficient to enhance excretion of certain transuranic radionuclides that people are likely to ingest or inhale after a radiological or nuclear event. Ca/Zn-DTPA, which is indicated for the decorporation of transuranic radionuclides (americium, curium and plutonium), is currently in the HHS/CDC Strategic National Stockpile. DTPA is administered daily by intravenous infusion. Therefore, the goal of this program is to develop a non-injectable form of DTPA which could be more easily administered and distributed in a large scale emergency. This promising technology has important considerations for a forward deployed radiation countermeasure for DoD personnel.

NIAID has also used Project BioShield authorities to announce the availability of grants for the development of new radionuclide decorporation agents for radiation/nuclear emergencies.

Members of the NIAID staff meet regularly with the research community at Fort Detrick and the United States Army Medical Research and Materiel Command, and with the staff of Armed Forces Radiobiology Research Institute (AFRRRI). Through such meetings, synergy in research and mutual support leading to the development of new drugs, vaccines, and diagnostic tests for the nation are achieved. NIAID personnel also hold meetings periodically with the Defense Threat Reduction Agency and the Defense Advanced Research Projects Agency, two important entities within the research infrastructure in the DoD.

Although NIH is a leading agency in government-sponsored research to develop medical countermeasures against biological, chemical, or radiological terrorist threats, it is by no means the only agency involved. The CDC, FDA, DoD, Department of Homeland Security (DHS), Department of Agriculture (USDA), DoE, and other governmental organizations also play important roles. Therefore, coordination among the

various agencies involved is extremely important. In broad terms, NIH-supported medical countermeasures research activities are coordinated using similar mechanisms, at three distinct levels: within NIH, within the HHS, and across the government as a whole.

Some of the medical countermeasures under development through HHS for the Strategic 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. DoD and HHS work cooperatively to leverage medical countermeasure programs of mutual interest and to ensure there is no funding redundancy.

Weapons of Mass Destruction Medical Countermeasures (WMD MCM) Subcommittee.

DoD actively participated on the interagency WMD MCM Subcommittee that defined requirements and set priorities for products that would ameliorate the effects of CBRN exposures. This Subcommittee assessed acquisition options, identified gaps in the product development pipeline, and made recommendations for addressing these gaps.

The WMD MCM Subcommittee reported to the Homeland Security Council's Biodefense Policy Coordinating Committee and Deputies Committee for informational and decisional briefings as necessary. The Subcommittee and its subordinate Working Groups included members from various Executive Branch agencies (DoD, USDA, HHS, DHS, VA, DOE, NRC, EPA, Homeland Security Council, National Security Council, Office of the Vice President, Office of Science and Science and Technology Policy, and OMB) and considered both civilian and military needs in their assessments.

The WMD MCM Subcommittee was responsible for evaluating the potential medical and public health impact of medical countermeasures on exposed populations. It achieved this by reviewing modeling scenarios of medical consequences and the effectiveness of medical response. Researchers use mathematical models to estimate casualties from an attack and its impact on the health care system. These models assess the effectiveness of various medical countermeasures, such as pre-event vaccination, post-exposure vaccination, post-exposure therapeutics, quarantine, and isolation. This process identifies knowledge gaps and helps to inform the medical countermeasures research agenda.

In 2007, the HHS created the Public Health Emergency Medical Countermeasures Enterprise Governance Board (EGB) to replace the WMD MCM Subcommittee. The DoD continues to participate in the EGB as an ex officio member of the board.

It is important to note that military and civilian requirements and concepts of use for medical countermeasures do not always match. Military capabilities requirements

generally focus on pre-exposure prophylaxis for a smaller, healthier population that will be put in harm's way. Civilian requirements focus on post-exposure prophylaxis or treatment for a larger, more diverse population. The military often needs products that uniformed service members can administer to themselves under field conditions, while civilian requirements tend to focus on those products that will be administered by first responders, nurses, and physicians. The route of administration for a product may differ based on the concept of use. For DoD, when a product must be self-administered the best route is often via an intramuscular injection. For civilians, where the concept involves first responders, nurses, or physicians to administer the countermeasure, intravenous injections may be the preferred route. This means that it is possible that countermeasures developed by HHS to suit civilian concepts of use may not be suitable for DoD for wartime use by service members.

Under Bioshield, there is provision for EUA to permit the effective use of promising medical countermeasures under development for treatments in an emergency if alternative treatments are not available. This will improve access by the public to a potentially beneficial treatment in an emergency situation, when it is most likely to save lives, even if it has not yet been fully approved by the FDA or is an approved product that would be used for a use not yet covered by an approved indication. In some instances, HHS may decide to forgo full FDA licensure and rely on EUA as a means to balance cost, schedule, and risk across their countermeasures portfolio.

DoD policy is to make preferential use of products already approved by the FDA for general commercial marketing to provide the needed medical countermeasures. When no FDA-approved product is available to meet a foreseeable threat, DoD will investigate conducting appropriate research and development program activities directed toward obtaining general commercial marketing approval by the FDA. Given the differing emphasis on FDA approval of products just discussed, each medical countermeasure must be considered separately to determine if it will meet interagency needs or will be developed by only one agency. When DoD considers transitioning a product to the HHS for advanced development, it must ensure that HHS intends to seek FDA licensure rather than choosing to use the product under the Bioshield EUA provisions. Should the DoD request approval of the Secretary of Defense to use a countermeasure as an investigational new drug (IND), the request must be justified based on the available evidence of the safety and efficacy of the drug and the nature and degree of the threat to personnel. When using INDs, the DoD must comply with 10 U.S.C. 1107, Executive Order 13139, and applicable FDA regulations.

Industry is unlikely to want to partner with DoD or HHS if the products they help develop can be used only under EUA. The investment in infrastructure to manufacture medical countermeasures with no assured means to recover their investments or garner profit is seen as an extremely risky approach by the commercial sector. Industry may undertake the early stages of development of bio-defense countermeasures on their own.

initiative. They are willing to assume a degree of risk of failure for early development efforts, but also want assurances that a market will exist for their products if they are successful in development and FDA licensure.

PROCUREMENT OF RADIATION MEDICAL COUNTERMEASURES

The DoD CB Defense Program (CBDP) jointly manages the research, development, and initial procurement of major CBRN defense equipment end items, certain expendable items, and selected vaccines. These items are funded through defense-wide funding accounts. Replenishment of consumable (Class II) CBRN defense items is managed by the Services and their Defense Logistics Agencies (DLA). The existence of defense-wide (rather than Service-specific) research, development, and acquisition funding accounts has ensured the joint integration of CBRN defense programs. However, no defense-wide (that is, joint) operations and sustainment funding mechanism exists for the sustainment of CB defense items, including replenishment and replacement of consumables. Because of this, the joint CB defense community is limited to tracking the status of the Services' defense logistics readiness and sustainment programs and making recommendations on funding issues.

DoD acquisition of FDA-approved CBRN medical countermeasures is a Service responsibility within their own budget. If a technologically mature product is available, it can be funded by the Defense Health Program. These technologically mature products (e.g., antithymocyte globulin, cytokines, hepatocyte growth factors) are then identified through the acquisition process with long-term funding.

The Services, JRO-CBRN Defense, the DLA, and the JPEO-CBD work in concert for the coordination and integration of joint CBRN defense logistics. The most challenging part of the joint acquisition process is joint sustainment. Understanding the operational environment is crucial to properly fielding and sustaining CBD items. Coordinating limited resources, gaining total visibility of CBD materiel, and ensuring that homeland defense requirements are considered, requires information sharing at unprecedented levels among all stakeholders. Unique commodity characteristics, such as the difference between a pharmaceutical product, a textile product, and a complex chemical or biodetection device, dictate a decision-making model which accounts for a diverse range of factors.

The JPM-CBMS acquisition strategy for all CBRN defense vaccines, therapeutics, and diagnostics is to buy commercially available FDA-licensed medical products. The JPM-CBMS develops products for the DoD or co-develops medical products with allied nations or other government agencies. RadCM development efforts are conducted through contracts with the medical industrial base. Developmental programs for medical countermeasures have also received multiple responses to requests for information and proposals that indicate a sufficient industrial base exists to support the CBMS mission.

The major issue in the pharmaceutical industry is concerns of legal liability over possible future side effects of the current generation of medical countermeasures. Legal issues and limited profitability keep many major pharmaceutical companies from producing for the defense market. Operation Enduring Freedom and Operation Iraqi Freedom are testing the capacity of the CBRN industrial base. The limitations of the industrial base are due in part to lowered DoD procurements in the 10 years leading up to the Global War on Terror (GWOT) and Operation Enduring Freedom. The limited procurements are due to low peacetime demand and budget restrictions. Also contributing to this problem is the inability of DoD agencies to commit to long-term contracts with CBRN defense firms.

In FY 2006 and FY 2007, an initiative was funded within JSTO-CBD to explore options for radioprotectants and related medical radiological defense countermeasures with a minimal investment (less than \$300,000), which was used as seed money to screen the efficacy of four to five steroid hormone, antioxidants, and free-radical scavengers in rodents. For FY 2007, after a market survey and extensive literature search, the JSTO-CBD evaluated 15 medical radiological countermeasures candidates for Milestone-A designation. During FY 2007, the JPM-CBMS evaluated these and other candidate compounds and will initiate advanced development activities on one candidate leading to eventual FDA approval. JPM-CBMS funding for RadCMs in FY 2008 is \$7 million.

FORWARD DEPLOYMENT

The Defense Medical Standardization Board (DMSB), formally known as the Joint Readiness Clinical Advisory Board (JRCAB), located at Ft. Detrick, in Maryland, is a joint activity under the direction, authority, and control of the ASD (HA). Since inception in 1945, the DMSB has been the focal point for medical materiel standardization within the DoD. The DMSB consists of flag and general officers who represent each of the military services, OASD (HA), the J4, DLA, and JFCOM. They are supported by a staff of clinicians, logisticians, pharmacists, information management, and support personnel from all Services. The DMSB identifies already accepted standard of practice medical countermeasures into the military treatment system. Many radiation medical countermeasures are already available and FDA-approved for use. For these standard-of-practice items, the DMSB identifies these products for placement into the military treatment system and the Joint Deployment Formulary (JDF).

The JDF is the recommended list of pharmaceutical products to be used and ordered by deployed and/or deploying forces. This list is continually updated to insure that that product is still the standard of care and is available for use and ordering. Several RadCMs on the JDF include hematopoietic growth factors such as Filgrastim (Neupogen) injection, a potent stimulator of hematopoiesis shortening the time to recovery of neutrophils.

RADIATION COUNTERMEASURE PLAN COST ASSESSMENTS

Assessing cost estimates for identifying, acquiring and forward deploying radiation medical countermeasures is problematic. Costs associated with bringing any one particular RadCM to FDA approval involves extensive science and technology efforts either through the DoD, partner Federal agencies, academia, private industry or a combination of any of these. As previously discussed, however, RadCMs produced and procured from other Federal agencies under the Economy Act, Title 31, United States Code (U S C), sections 1535 and 1536 will likely result in lower costs to the DoD than anticipated.

Additionally, the Services will likely bear 70 percent of the funding for RadCM acquisition with ASD (ATL) providing the remaining 30 percent. Funding identified for chemical and biological medical countermeasures cannot be used for non-chemical and biological acquisition (i.e., RadCM).

Since the JCIDs requirements process for radiation medical countermeasures is uncompleted, a structured capabilities-based assessment (CBA) that defines capability gaps, capability needs and approaches to provide those capabilities within a specified functional or operational area is absent and the acquisition community is unable to define costs associated with procurement of radiation medical countermeasures at this time.

Medical defense materiel centralization/decentralization for the Services deployed forces, stockpile requirements, and the DOD/FDA Shelf Life Program are all sufficiently described in the Department of Defense Chemical And Biological Defense Program (CBDP) Annual Report to Congress of April 2007.

Finally, the FY 2008 President's Budget Submission for the DoD CBDP does build on the existing capabilities fielded to protect U S forces against CBRN threats. The CBDP budget provides a "balanced investment strategy" that includes investment in procurement of capabilities to protect U S forces in the near-term (FY 2007-FY 2008). The Department, as part of its FY 2009 budget process, will review making investments in advanced development to protect U S forces in the mid-term, and investments in basic research and the science and technology base to protect U S forces through the far-term and beyond. In addition, the FY 2008 budget continues support of an increased investment in the test and evaluation infrastructure necessary to maintain the technological advantage against emerging threats. The investment in the science and technology base and the supporting infrastructure will yield advanced capabilities that will continue to be fielded through the far-term.