Crossing the Valley of Death: Bringing Promising Medical Countermeasures to Bioshield
Bill Number:
Hearing Date: June 9, 2005, 2:00 pm
Location: SD430
Witness:
Dr. William F. Raub
Department of Health & Human Services
Deputy Assistant Secretary for Public Health Emergency Preparedness
Testimony

Good afternoon, Mr. Chairman, Senator Kennedy and Subcommittee members. I am William Raub, Deputy Assistant Secretary for Public Health Emergency Preparedness, Department of Health and Human Services (HHS). I am here with my colleague, Dr. Carole Heilman, Director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH). We appreciate the opportunity to share with you information on our progress in implementing the Project BioShield Act of 2004, which was enacted in July 2004. Biodefense is a top priority for the Bush Administration and having an appropriate armamentarium of medical countermeasures is a critical aspect of the response and recovery component of the President's strategy "Biodefense for the 21st Century." The acquisition and ready availability of medical countermeasures, such as antibiotics, antivirals, monoclonal and polyclonal antibodies against infectious threats; therapies for chemical and radiation-induced illnesses; and vaccines to protect against biological agents and toxins will have a substantial impact on our preparedness and response capabilities.

Protecting Americans

The events of September and October 2001, made it very clear that terrorism—indeed bioterrorism—is a serious threat to our Nation and the world. The Bush Administration and Congress responded forcefully to this threat by seeking to strengthen our medical and public health capacities to protect our citizens from future attacks. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 substantially increased funding authorization for the Centers for Disease Control and Prevention's (CDC's) Strategic National Stockpile. To encourage the development of new medical countermeasures against biological, chemical, radiological and nuclear agents and to speed their delivery and use in the time of an attack, President Bush, in his 2003 State of the Union address, proposed, and Congress subsequently enacted, the Project BioShield Act of 2004. Project BioShield authorized the use of the Special Reserve Fund created in the first Department of Homeland Security (DHS) appropriation bill (P.L. 108-90) in October 2003. This $5.6 billion appropriation is designed to assure developers that funds will be available to purchase critical medical countermeasures to protect our citizens. In addition, over $5 billion in biodefense funding was appropriated to NIH between FY 2002 and FY 2005. These funds have provided significant support of research and development of safe and effective medical countermeasures.

The Strategic National Stockpile Today

The wake-up call that we received in the fall of 2001 brought clarity to the gaps in our

medical countermeasure armamentarium and we immediately sought to address these gaps. Although much remains to be done, we have made significant progress in building our Strategic National Stockpile (SNS). For example, our smallpox vaccine stockpile has grown from 90,000 ready-to-use doses in 2001 to enough vaccine to protect every man, woman, and child in America. Major strides have been made in building our medical countermeasure antibiotic reserve against anthrax, plague, and tularemia. The SNS now contains countermeasures to protect and treat millions of Americans in the event of an attack with one of these agents. We have also built our stockpile of countermeasures to address the effects of radiation exposure with products such as Prussian Blue and diethylenetriaminepentaacetate (DTPA). These countermeasures act to block uptake or remove radioactive elements such as cesium, thallium, or americium from the body. Potassium iodide, a drug that can protect the thyroid from the harmful effects of radioactive iodine, is also stockpiled in formulations that will protect both adults and children. Furthermore, under Project BioShield, HHS is acquiring licensed and next-generation anthrax vaccines as well as anthrax antitoxins to further enhance our capabilities to respond to that threat. We have taken the botulinum antitoxin research program started by the Department of Defense (DoD) in the early 1990s to completion and we are now in the process of adding to our stockpile of botulinum antitoxins.

Ongoing Project BioShield activities at NIH and HHS

The Project BioShield Act of 2004 created several mechanisms to help the United States Government (USG) address gaps in the medical countermeasures development pipeline. These mechanisms include new authorities for the NIH to expedite the research and development of promising medical countermeasures in advance of the acquisition of these countermeasures through the Project BioShield.

Last month, the NIAID announced the first awards made using its new BioShield authorities. These awards included ten grants and two contracts totaling approximately $27 million to support the development of new therapeutics and vaccines against some of the most deadly diseases that could be caused by bioterrorism, including anthrax, botulism, Ebola hemorrhagic fever, pneumonic plague, smallpox and tularemia. These grants and contracts, which range in duration from twelve to eighteen months, respond to a key objective of the NIAID biodefense research agenda that emphasizes the development of new and improved medical products against agents identified by the CDC as Category A agents, those deemed to pose the gravest threat.

In addition to these medical countermeasures development contracts, several BioShield procurement activities are underway at HHS. The Office of Public Health Emergency Preparedness (OPHEP) is reviewing the responses to Requests for Proposals (RFPs) for anthrax therapies, and is continuing to move forward on the acquisition of an antitoxin treatment for botulism. Furthermore, OPHEP has signaled its intent to acquire a next generation smallpox vaccine by releasing a draft RFP for industry comment. The smallpox vaccine development and acquisition program exemplifies the strong partnership between NIAID and OPHEP for this medical countermeasure. This development program has been closely monitored within HHS, and the requirements and options for acquisition were developed by the interagency Weapons of Mass Destruction (WMD) Medical Countermeasures subcommittee.

Finally, in anticipation of yet-to-be-determined requirements, OPHEP, in coordination with colleagues throughout the USG, actively monitors the state of the medical countermeasure pipeline-- both within and outside the government--- by evaluating USG research and development portfolios and engaging industry through the publication of Requests for Information (RFIs). For example, OPHEP has released three RFIs to assess the timeline to maturity of medical countermeasures to treat nerve agent exposure, acute radiation syndrome, and additional products that might be available to treat anthrax. These RFIs are a key tool for HHS to dialogue with industry partners and to inform the development of sound USG acquisition strategies.

Development of Medical Countermeasures

These accomplishments in acquiring needed countermeasures for the Strategic National Stockpile were possible in large part because of substantial existing research and development of countermeasures in these key areas. The development of medical products —whether for cancer, influenza, or anthrax – is a complex, lengthy, and expensive process. An overview of the key features and challenges of the medical countermeasure pipeline from concept to regulatory approval may be helpful to understand the complexity of the process.

Steps in medical product development

The initial stage in the medical countermeasure pipeline is a robust basic research program. The milestones at this stage include a fundamental understanding at the molecular level of host-pathogen interactions, the pathogenicity of the threat agent, identification of targets of opportunity for preventing or mitigating the consequences of the threat agent, and determining the mechanism of action of potential medical countermeasure candidates. The following stage is described as applied research; here, candidate products are identified and screened for activity against a threat agent, and animal models are developed. In the development stage, processes are established to manufacture the product using current Good Manufacturing Practices (cGMP) and human clinical Phase I and Phase II trials are conducted. These clinical trials and additional animal efficacy studies enable the determination of optimal formulation and dosage schedules. In addition, the stability profile is evaluated and a large-scale, validated manufacturing processes with requisite quality control/quality assurances is established. In the final development stage, production and licensure, Phase III trials and pivotal animal studies are completed. Ultimate licensure, approval or clearance from the U.S. Food and Drug Administration (FDA) requires the rigorous accumulation of sufficient data in humans and animals to establish the safety and efficacy of the product and the ability to consistently manufacture the product to meet the standards of cGMP. It is important to note that a unique aspect of the pathway for medical countermeasures is the need to establish efficacy either using surrogate markers (such as the human immune response) or, using appropriate animal models, under the “Animal Rule” because demonstration of efficacy against the actual diseases in humans is most often not feasible either because the disease does not occur naturally or for the obvious ethical reasons that prevent exposing humans to the threat agent.

Challenges to product development

The pathway from medical product concept to a safe, effective, and reliably manufactured product suitable for regulatory approval can be a long and expensive one. Studies indicate that each new product brought to market can take up to a decade of development and up to a billion dollars of investment; the overwhelming number of candidates will fail before one is found that demonstrates sufficient evidence of safety and efficacy to justify approval, licensure or clearance by the FDA. For example, a new drug compound entering Phase I testing, often representing the culmination of upwards of a decade of preclinical evaluation, is estimated to have only an eight percent chance of reaching the market.

The Strategic Approach to Addressing Medical Countermeasure Gaps

With the critical path for medical countermeasures in mind, the USG has taken a strategic approach to the development and acquisition of these countermeasures. The initial focus of our efforts to protect the Nation was aimed largely at those threats that could do the greatest harm to the greatest number of our citizens, namely, smallpox and anthrax. Our national security environment demands accelerated product development timelines and new paradigms of interactions between industry and government with increased risk-sharing and enhanced intra-governmental collaboration. Using a robust interagency process that mined intra- and extra-governmental expertise, requirements for medical countermeasures were identified, and options elaborated for addressing immediate and long-term needs. In addition, there have been substantial interagency efforts within HHS to examine and address gaps in the pipeline. Experts from throughout HHS and USG continue to define the most expeditious way to traverse the critical pathway to develop and acquire safe and effective medical countermeasures for the Strategic National Stockpile. This approach is focused on identifying and addressing gaps in this critical pathway.

Addressing Critical Countermeasure Gaps for Anthrax and Smallpox

The USG actions taken to fill gaps in our anthrax and smallpox armamentarium best illustrate the outcome of our strategic approach in the development medical countermeasures and the implementation of the Project BioShield Act of 2004.

Anthrax

Although anthrax is not transmissible from person-to-person, an attack involving the aerosol dissemination of anthrax spores, particularly in an urban setting, is considered by public health experts to have the potential for catastrophic effects. The potential for large-scale population exposure following aerosol release of anthrax spores, the reality of the threat demonstrated by the anthrax letters of October 2001, and our knowledge that anthrax has been weaponized by state-actors, highlight the nature of the threat. Following the process established by Project BioShield, the Secretary of the Department of Homeland Security (DHS) determined that anthrax posed a material threat to the Nation, and, because untreated inhalation anthrax is usually fatal, the Secretary of HHS identified anthrax as a significant threat to public health. It is for these reasons that three of the first six acquisition programs under Project BioShield have been targeted to address this pathogen.

The approach to protect citizens against this threat demanded immediate, intermediate and long-term strategies and requirements. The NIH and HHS are working aggressively to address the requirements, many of which are defined by the interagency WMD Medical Countermeasures Subcommittee. These requirements are informed by material threat assessments provided by the DHS. First, the existing stockpile of antibiotics against anthrax in the Strategic National Stockpile was increased. Second, there is a need for an anthrax vaccine to be used not only for pre-exposure protection for laboratory and other workers at known risk for anthrax, but also for use concurrently with antibiotics after an exposure. Anthrax spores are stable in the environment and would have a profound impact if released in an urban population. Availability of an anthrax vaccine is a critical requirement for restoring the functionality of any exposed area. Finally, an anthrax vaccine and anthrax therapeutics such as antitoxins would provide for protection and treatment of individuals exposed to an engineered strain of anthrax that may be resistant to antibiotics.

In a 2002 report, "Anthrax Vaccine: Is It Safe? Does it Work?", the Institute of Medicine recommended that a new vaccine be developed according to more modern principles of vaccinology. To address this gap, NIH convened experts in the fall of 2001 to assess developing technologies. Based on their review, HHS decided that there was a sufficient scientific foundation to support the aggressive development of a next generation anthrax vaccine consisting of recombinant protective antigen (rPA). The research on rPA, spanning more than a decade, was conducted in large part by the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland.

HHS defined a three-stage development and acquisition strategy to address the gaps in anthrax countermeasures through a public-private partnership model using open competition for awards at each stage. The early and advanced development programs for rPA were supported by the NIAID with contract awards in September 2002 and 2003, respectively. These were milestone-driven contracts with well-defined deliverables including the manufacture of clinical-grade vaccine, the conduct of Phase I and Phase II clinical trials, and consistency lot manufacturing of vaccine. Demonstrated large-scale manufacturing capability would be required to support the initial civilian acquisition target for rPA, which was defined through an interagency process to be the protection of 25 million persons. Senior officials from several Departments of the USG evaluated acquisition options to fulfill this target and, in the fall of 2003, agreed to pursue this acquisition of rPA anthrax vaccine.

An evaluation of the NIAID rPA anthrax vaccine development program indicated that it was robust enough to suggest that rPA vaccine could potentially become a licensed product within eight years. In March 2004, the acquisition program for this vaccine, under the direction of the OPHEP, was launched, relying on the Special Reserve Fund. Utilizing a robust technical and business evaluation process, OPHEP reviewed multiple proposals and negotiated a contract for 75 million doses of the vaccine. This contract uses a milestone and deliverables approach to lay out an ambitious program which includes the delivery of the first 25 million vaccine doses to the Strategic National Stockpile

within 2 years of contract award. A unique and critical aspect of the rPA vaccine BioShield acquisition contract is the fact that no payment will be made until a usable product is delivered to the Stockpile. While awaiting delivery of this new vaccine to the Stockpile, OPHEP negotiated a contract for five million doses of the currently licensed anthrax vaccine to support immediate requirements. Delivery of that product to the Stockpile has already begun. Over one million doses of the licensed anthrax vaccine are now in the Stockpile.

Smallpox

A similar three-stage development and acquisition strategy was utilized to address the gap regarding a next generation smallpox vaccine. The interagency WMD Medical Countermeasures Subcommittee defined a requirement for this product that addressed the millions of U.S. citizens who have contraindications for the existing smallpox vaccines in the absence of exposure to smallpox. One candidate next-generation smallpox vaccine, modified vaccinia Ankara (MVA), is based on a strain of the smallpox vaccine virus that, in contrast to current smallpox vaccines such as Dryvax, does not replicate effectively in human cells and may cause fewer side effects. The development programs for MVA were supported by the NIAID with milestone-driven contract awards in 2003 and 2004. Early clinical trials in limited numbers of human volunteers have demonstrated the MVA vaccine to be safe and immunogenic, and animal studies by the developers are confirming earlier studies by NIAID and DoD scientists showing that MVA protects monkeys and mice from smallpox-like viruses. Based on these results and the demonstration of the feasibility of large-scale manufacturing capacity, HHS has moved forward with the initial stages of an MVA acquisition program. A draft RFP was released last month; the final RFP will be released following review of industry comments.

Priority Setting Beyond Smallpox and Anthrax

The approach taken to rapidly expand our Nation's response capacity to meet the medical and public health impact of either a smallpox or anthrax attack demonstrate our national resolve to address these high priority threats. However, in many ways, anthrax and smallpox vaccines represent the "low hanging fruit" for medical countermeasure research; development and acquisition were enabled by a substantial research base developed by USAMRIID and NIH. There was consensus that these were our highest priorities and there were countermeasures available or relatively far along in the development pipeline to permit acquisition for the SNS. Given an almost endless list of potential threats and with finite resources to address them, prioritization of these threats and appropriate countermeasures is essential to focus our efforts. We rely heavily upon our interagency partner, the DHS, to provide us with a prioritized list of threats along with material threat assessments that will provide reasonable estimates of population exposure. This information is critical for future strategic decision making regarding how best to focus our National efforts in countermeasure development and acquisition, including whether in the short-term, the so-called "one-bug, one-drug" approach should continue while simultaneously investing in more broad-spectrum prevention and treatment approaches for the longer term. These issues are actively being addressed by the interagency WMD Medical Countermeasures Subcommittee.

Coordinating efforts to fill gaps in the critical path to needed countermeasures
HHS is strengthening existing intra- and interagency partnerships and creating new ones that are needed to address identified gaps in the Nation's medical countermeasure research, development, and acquisition pipeline. A key collaboration is between OPHEP and NIAID, with contributions from FDA in high priority areas. Senior scientific and policy staffs from these organizations meet regularly to discuss identified gaps and outline strategies to address these gaps using existing institutional structures and resources.

Addressing Medical Countermeasure Gaps for Chemical and Radiological/Nuclear Threats
For the development of medical countermeasures to address chemical, radiological and nuclear threats, OPHEP, NIH and FDA have established a unique partnership in which experts from these organizations meet on a regular basis to identify appropriate targets and conduct joint planning that ensures the alignment of development and acquisition priorities.

In 2004, HHS tasked NIAID with developing a research program to accelerate the development and deployment of new medical countermeasures against ionizing radiation for the civilian population. NIAID worked to build upon prior experience and ongoing research efforts as it gathered input from across the USG as well as from experts in industry and academia to inform the development of a planning document, entitled The NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats. This document is in the final stages of production and will be made available shortly.

This Strategic Research Plan and Agenda is organized into four sections: (1) basic and translational research on the mechanisms of radiation injury, repair, and restoration that can lead to the identification and characterization of new therapeutics; (2) bioassays and tools for biodosimetry, which will aid in diagnosis; (3) immediate product development of promising therapies; and (4) infrastructure to support the necessary research. The document is intended to unify and strengthen the research community focused on these areas, promote increased collaboration, and facilitate transition from research to product development. NIH will work closely with OPHEP to prioritize the research and development activities to align with the priorities for acquisition under Project BioShield.

The FY 2005 funding for NIH radiation countermeasures research is $47 million; these funds are provided through an appropriation to OPHEP. A proposal for specific project commitments was submitted by NIH and reviewed and approved by OPHEP. Proposed projects include:
• a network of research facilities called the Centers for Medical Countermeasures for Radiation;
• contracts to support the development of orally-available forms of calcium and zinc DTPA, which enhance the excretion of certain radionuclides that would be released by a nuclear device or as a result of an attack on a nuclear reactor;
• a contract to support a broad range of product development activities;

• an interagency partnership with the Armed Forces Radiobiology Research Institute of the DoD; and
• an initiative to support projects that explore ways to protect the immune system from radiation damage.

This program will be guided by a Program Management Team comprised of representatives from NIH and OPHEP. The projects will be directed by staff in NIAID's Division of Allergy, Immunology, and Transplantation.

Similarly, NIH was tasked by HHS to draft a strategic plan and research agenda to guide the development of medical countermeasures against chemical threats. In FY 2006, $50M from the Public Health Social Services Emergency Fund is requested for this purpose. Following the oversight and planning model established for radiological and nuclear medical countermeasures, a Program Management Team with representatives from NIH and OPHEP will be established and a spending plan will be developed prior to the allocation of funds. Some of the objectives targeted for development will include anti-seizure medications, rapid diagnostics, animal models and decontaminants. A Strategic Plan and Research Agenda from NIH is expected to be completed by the end of this calendar year.

Novel and Emerging Threats
The initial efforts for medical countermeasure development and acquisition have been rightfully focused on those threat agents known to have the potential to cause catastrophic effects on our nation and its citizens. In addition, HHS and NIH are keenly aware of, and invest efforts to address threat agents that we might face in the future, including engineered threats.

As is also the case for the known threat agents, we are dependent upon our colleagues at DHS to identify and prioritize these threats. One of the most recognized potential engineered threats is antibiotic-resistant anthrax, and the HHS, NIH and FDA accomplishments to date in facilitating the development and acquisition of anthrax vaccines and therapeutic antitoxins have an important beneficial impact on reducing our vulnerabilities. In addition, NIH has a robust investment in the development of novel antimicrobial agents and in addressing all aspects of antibiotic resistance, including the development of antibacterial agents that could potentially be useful against a broad spectrum of species and a wide range of drug resistance mechanisms and is working with the DoD, to leverage medical countermeasure programs and resources of mutual interest. Several medical countermeasures now being developed through NIAID for civilians have their technology basis in programs which originated in DoD.

One major NIAID basic biodefense research initiative is focused on the human innate immune system, which is comprised of broadly active "first responder" cells and other non-specific mechanisms that are the first line of defense against infection. The development of methods to boost innate immune responses could lead to the development of a relatively small set of fast-acting countermeasures that would be effective against a wide variety of pathogens, including engineered threat agents.

Conclusion

In closing, I must emphasize that the number of threat agents against which we could guard ourselves is endless. New and emerging threats introduced by nature or by design will present continuing challenges. Although we cannot be prepared for every threat, we have the ability to create a strategic approach to identifying and combating the greatest threats through the development and availability of safe and effective medical countermeasures. HHS and its agencies, including NIH, CDC, and FDA, have a clear mandate from President Bush and Congress to lead the charge in this arena and in the implementation of Project BioShield. The tightly orchestrated development, acquisition, and review programs for next generation anthrax and smallpox vaccines outlined here are outstanding demonstrations of the USG support and management of a medical countermeasure program throughout the development pipeline.

We have already made important strides and will continue to work to address the obstacles identified. Mr. Chairman, I look forward to working with you and members of the Subcommittee to address the challenges of bioterrorism preparedness and its impact on public health.

We will be happy to answer any questions you may have.