DEFENSE HEALTH BOARD
FIVE SKYLINE PLACE, SUITE 810
5111 LEESBURG PIKE
FALLS CHURCH, VA 22041-3206

APR 29 2009

DHB

MEMORANDUM FOR: SURGEON GENERAL OF THE ARMY

SUBJECT: Defense Health Board Task Force Review of the Department of Defense Biodefense Infrastructure and Biological Research Portfolio

EXECUTIVE SUMMARY

In a memorandum dated 3 October 2008, the Surgeon General of the Army LTG Eric B. Schoomaker requested that an Ad Hoc Subcommittee of the Defense Health Board (DHB) be established to review the Department of Defense (DoD) biodefense infrastructure and research portfolio, and specifically address the following three questions:

- Whether there is a national and/or strategic defense need for the Military Service Departments (MSD) to own and operate an infrastructure in support of mission requirements for defense capabilities (abroad and homeland) for biodefense.

- Whether the current processes are effective in transferring the results of basic biological research to advanced product development and licensure.

- Whether the current infrastructure provides scientific or strategic return on investment for previous and current research, design, test and evaluation (RDT&E) efforts.

The interim report reflects the Task Force's provisional findings and recommendations based on a review of unclassified material restricted to biologic biodefense products.

I. Need for the Military Service Departments (MSDs) to Own and Operate an Infrastructure in Support of Mission Requirements for Defense Capabilities (Abroad and Homeland) for Biodefense:

Upon a review of the literature and information presented, the Task Force found an indisputable need for the DoD to own and operate an infrastructure in support of biodefense capabilities, based on, but not limited to, the following:

- Benefits of DoD biodefense laboratories extend beyond the service member to impact national defense, have the unique ability to provide a surge capacity and promptly respond to bioterrorist events, and realign assets for high-priority missions as a result of significant investment in facilities, knowledge and personnel.

- DoD biodefense laboratories have the capacity to respond to the high demand for Biosafety Level Four (BSL-4) containment laboratories (especially with regard to animal efficacy studies).

- Specific examples of unique military laboratory capabilities include: novel threat agent (NTA) test chambers; aerosol and aeromedical isolation capabilities; and, unique critical agent and culture archive assets.

- DoD biodefense laboratories have unique capabilities of the DoD to leverage both industry and academia.

- Several disincentives and impediments exist within the academic and industry setting to engage in biodefense research including: the risk involved in working with and maintaining select agents; lack of profit motive or incentives for investment for "orphan" vaccines; high costs for security and operations and hazardous agent research; absence of in-house expertise and equipment (including containment operations); and, a shift in the traditional research focus to one of deterrence and threat reduction.

II. Effectiveness of Current Processes in Transferring the Results of Basic Biological Research to Advanced Product Development and Licensure:

While basic science research is sound, barriers toward advanced product development and licensure exist, and affect both the efficacy and efficiency of a successful system that results in product development, and a successful effective maintenance of capabilities to respond to current and future biological threats. The Task Force recognizes several challenges regarding product licensure impacting the efficiency and effectiveness of the licensure process for investigational new drugs (INDs), including but not limited to the following:

- Various constraints on research are imposed by the Food and Drug Administration (FDA) "animal rule," including: increased costs, the requirement of additional data, and development of an appropriate animal model, which ultimately support few product candidates a year and possibly impact readiness levels.

- The substantial increase in costs over time for pharmaceutical product development is due to FDA regulatory demands, increasing costs of research equipment, clinical trial size and complexity, and patient recruitment and retention in clinical trials. These factors are exacerbated by the limited commercial market for most biodefense pharmaceuticals.

- Effective, synergistic collaborations need to be established to optimize the use of available resources and specific highly-developed expertise in the civilian private and academic sectors.

- Recruitment and retention of personnel with appropriate experience and expertise are critical to maintaining a sound infrastructure capable of efficient product development.

- Accountability for performance should be established and efforts pursued to ensure the capability of a well-trained work force.

- Due to the significant financial investment and magnitude of people affected, DoD biodefense research programs should be tightly-focused and state-of-the-art, with transparent and well-defined priorities, timelines, and accountabilities, and a clear and timely ROI to both the warfighter and the Nation.

- In the presence of rapidly changing threats, the biodefense programs should be flexible and able to realign given swiftly changing priorities and a lack of commercial interest.

Separate lines of funding from different entities are not amenable to long-term project sustainability. In addition, funding for licensed biodefense biologics will not be fully supported by the industrial sector and must come from the DoD. In addition, the Task Force concluded that:

- A thorough evaluation should be conducted regarding realistic endpoints in regards to licensed FDA products, for many of the specialized vaccines that DoD needs to have available and for which the private sector does not require or support.

- Since it is neither feasible nor realistic to have adequate funding to license many such products, the U.S. government including the FDA and DoD, need to reevaluate the endpoints of the vaccine program as a major policy question. Defining the endpoints to be more realistic is critical.

The Task Force received briefs and documents pertaining to the Transformational Medical Technology Initiative (TMTI), and concurs that this approach is an innovative attempt at determining whether the industry model of management is practical in the realm of DoD's biodefense product research and development. In addition, the Task Force recognizes that TMTI has a role in facilitating interagency cooperation and development. Effective execution of TMTI has aided in the transition of products to IND status, the origination of sequencing capabilities, and core platform development.

III. Scientific or Strategic Return on Investment (ROI) of Current Infrastructure:

Based on an initial review, the Task Force recognized several objective markers of considerable return on investment (ROI), but felt that:

- No systematic evaluation metrics, processes, or procedures were evident to evaluate programs.

- In addition, with the transition from a goal to "develop products to the IND state" to "develop FDA-licensed products," the personnel, processes, expectations, and progress required are unclear.

- The Task Force believes further effort should be expanded into the measurement, tracking, and evaluation of programs, processes, and procedures in place in order to optimize efficiency and maximize ROI. These include the establishment of well-defined metrics; the monitoring and tracking of results over time; the methodical reporting of results; and, a well-defined mechanism to eliminate non-productive programs.

In addition to the findings detailed above, the Board recommends:

- **The DoD biodefense infrastructure should be retained. Further attempts should be made to create a national integrated biodefense campus in order to ensure accountability, enhance stronger leadership, and reduce costs and redundancies.**

- **Medical countermeasures should be made a priority within the Department, and effective, synergistic collaborations established and incentivized to optimize the use of available resources and specific highly-developed expertise in the private and academic sectors. In particular, collaborations involving federal agencies, academia, and industry should be further developed, incentivized, and accelerated.**

- **An adequate funding process to include realistic time lines and multi-year funding agreements must be ensured to meet the demands and challenges of the regulatory process.**

- **Due to the significant financial investment and magnitude of people affected, DoD biodefense research programs should be tightly-focused and state-of-the-art, with transparent and well-defined priorities, timelines, and accountabilities, and a clear and timely ROI to both the service member and the Nation.**

- **In the presence of rapidly changing threats, the biodefense programs should be flexible and able to realign given swiftly changing priorities and a lack of commercial interest.**

- **Biodefense research program planning within the Department should be centralized and "joint" to optimize the long-term success in developing and deploying novel biodefense products.**

- **DoD biodefense research priorities should be made explicit and transparent.**

- **External scientific review and input need to be expanded and amplified.**

- **Systematic scientific progress and ROI metrics to evaluate programs and terminate biodefense research projects should be established or made evident.**

- **It is critical that sustained and identifiable performance accountability be implemented and efforts pursued to ensure leadership and work force capabilities.**

- **Mechanisms to provide education and training for future DoD biodefense scientific leadership must be established.**

- **Recruitment and retention of personnel with appropriate experience and expertise are essential to maintaining a sound infrastructure capable of efficient product development.**

- **TMTI is a novel experiment, and its results should be evaluated and if successful, generalized throughout DoD.**

- **To ensure appropriate efforts regarding biosurety, an authorized red team should be charged with defining and exploiting vulnerabilities.**

- **Given the restricted time frame within which this Task Force developed these initial recommendations, the Board recommends the DHB Task Force further engage in a more comprehensive overall evaluation of the DoD biodefense infrastructure and biological research portfolio.**

Our observation is of highly dedicated, hard-working scientists and administrators determined to make a difference – but in the context of a major change of mission to developing FDA approved products - who are now failed by a slow system that tolerates complexity, lack of clear priorities, inadequate accountability, redundancy, inadequate funding, and lack of experienced leadership.

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n. Presentation: Defense Threat Reduction Agency (DTRA) Chemical and Biological Technologies Directorate, to the Defense Health Board (DHB), 7 November 2008, by Mr. John Connell, Special Assistant, DTRA and Science and Technology Program Manager at Department of Defense.

o. Presentation: Chemical Biological Medical Systems Overview: Chemical and Biological Medical Systems, to the Defense Health Board (DHB), 7 November 2008, by Mr. Rick Nidel, Acting Joint Product Manager, Joint Vaccine Acquisition Program, Chemical ad Biological Medical Systems.

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- Whether the current processes are effective in transferring the results of basic biological research to advanced product development and licensure

- Whether the current infrastructure provides scientific or strategic return on investment for previous and current research, design, test and evaluation (RDT&E) efforts

BACKGROUND:

The DoD research, design, test, and evaluation (RDT&E) infrastructure supports particular mission requirements and ensures military capability to operate in a chemical/biological defense setting. The infrastructure augments the Office of the Secretary of Defense's Chemical and Biological Research, Development and Acquisition Program, and includes various facilities in the United States and abroad conducting research on select agents and other biological and chemical threats to military personnel. Concerns arise regarding whether the portfolio of biodefense research conducted within the Department is necessary, balanced, and effectively focused to meet National Security needs, while protecting and sustaining the health and combat-readiness of service members.

The DHB established a Task Force to examine these issues, and held a teleconference on 24 October 2008 and an in-person meeting on 7 November 2008, to receive briefs from the Defense Threat Reduction Agency (DTRA), Joint Program Executive Office (JPEO), Office of the Special Assistant for Chemical & Biological Defense and Chemical Demilitarization, as well as the Departments of the Army, Navy, and Air Force. On behalf of the Subcommittee, Dr. Poland, Task Force Chair and DHB President, and Dr. Clements, Task Force member, participated alongside Flag Officers in site visits to the Edgewood Chemical and Biological

Center, Walter Reed Army Institute of Research (WRAIR), and the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), on 19 November 2008.

The interim report below reflects the Task Force's provisional findings and recommendations based on a review of unclassified material restricted to biologic biodefense products.

SPECIFIC FINDINGS

Need to Own and Operate Biodefense Infrastructure

Determination of Need for Infrastructure

Based upon the information presented, the DHB Task Force agrees unequivocally that there is a need for biodefense infrastructure within the DoD to support domestic and international mission requirements. Factors identified by the Task Force that warrant the maintenance of this infrastructure within the Department include the:

- Uniqueness of the biodefense portfolio to investigate threat agents
- Focus of Service laboratories on the warfighter
- Unparalleled responsiveness of military laboratories to military threats and national security needs as a result of the significant investment in facilities, knowledge and personnel
- Ability to apply medical technology to specific military relevant problems
- High demand for Biosafety Level Four (BSL-4) containment laboratories (especially with regard to animal efficacy studies)
- Unique capabilities of the DoD to leverage both industry and academia, respond to emerging threats, and develop therapeutics

Specific examples of unique military laboratory capabilities include:

- Novel threat agent (NTA) test chambers
- Aerosol and aeromedical isolation capabilities
- Unique critical agent and culture archive assets

- Special Immunization Program, where products lacking a commercial market are used for protection of at-risk biodefense laboratory workers

Furthermore, specialized military facilities engaged in biodefense research are capable of realigning assets for high-priority missions and providing a rapid response and a surge capacity, especially after major terrorist events such as the anthrax attacks in 2001, which involved the United States Postal System and drastically elevated the nation's awareness of potential biowarfare threats. The growing threat of exposure to biological weapons by terrorists or during combat demands effective countermeasures. As a result, a priority emerged to enhance the nation's biodefense research capabilities and to form a sound and comprehensive national strategy to develop countermeasures to protect civilians and the military against biological threats. In addition, other government agencies, such as the Federal Bureau of Investigation, the Centers for Disease Control and Prevention, the World Health Organization, and the U.S. Postal Service rely on the information and support provided by the scientific and technical (S&T) programs of DoD biodefense laboratories.

The DoD biodefense mission is conspicuously distinct from that of the private sector in that it requires each novel biodefense agent be assessed for military relevance – the extent to which such capability will allow the military the ability to detect and sample for biological threat agents in the environment, and pursue combat operations in a biologically contaminated environment.

Furthermore, several disincentives and impediments exist within the academic and industry setting to engage in biodefense research relevant to DoD needs, including the:

- Risk involved in working with and maintaining select agents and the lack of ability or willingness to comply with select agent requirements

- Lack of a profit motive or incentives for investment from the pharmaceutical industry for "orphan" vaccines

- High costs for security and surety-oriented operations and for participating in research involving hazardous agents (including the legal costs associated with these potential hazards)

- An absence of in-house expertise and equipment (including containment operations)

- Shift in the traditional research focus to one of deterrence and threat reduction

As a result, much of the research conducted by the military may not be executed in an academic setting. For example, biodefense research areas of focus by WRAIR include medical countermeasures for genetically engineered threats. In addition, approximately 70% of the research conducted at USAMRIID has been on a BSL-4 level. Furthermore, USAMRIID's diagnostic capability supports DoD and other national efforts to protect against bio-threats by

participating in the Centers for Disease Control and Prevention (CDC) laboratory response network and having the ability to operate as a CDC back-up facility. In addition, there is no financial incentive for the private sector to consistently maintain and sustain a viable biological defense infrastructure. Therefore, in order to ensure that a national capability is maintained, DoD has relied primarily on the research expertise and facilities of the Services to address biological threats.

Service Compliance with Mission Requirements for Ownership and Operation of Biodefense Research

The Task Force received information and briefs pertaining to whether an overlap exists between the DoD, the Department of Health and Human Services (DHHS), and other Federal Agencies. The Department of Homeland Security (DHS) and DHHS have medical countermeasure partnerships where there is "unity of purpose" in requirements and capability, including: achievement of Food and Drug Administration (FDA) licensure; leveraging of BioShield and DoD funding; use of Economy Act purchases once licensed by the FDA; as well as the initiation of interagency agreements. The Task Force also learned that following the terrorist attacks on September 11, 2001, there has been some convergence of military and civilian biodefense requirements, including vaccination and treatment for: anthrax, smallpox, Ebola/Marburg, nerve agents, as well as treatments for Tularemia, Botulism, and radiation exposure. However, while the primary focus of the DoD is protecting forces prior to exposure, that of the DHHS is on post-exposure threat response that affects the general civilian population.

The Task Force received briefings regarding the recent initiative to integrate the biodefense portfolios of the Department of Defense and the Department of Health and Human Services, collectively entitled the Integrated National Portfolio. A stated purpose of combining an end-to-end national biodefense portfolio for medical countermeasure products is to leverage investments and achieve success, while maximizing end-to-end prevention, preparedness, and response objectives. In addition, the management of the Integrated National Biodefense Medical Countermeasures (MCMs) Portfolio must be informed by industry benchmarks for MCM development, while systematically addressing identified threats and required capabilities. Currently, no single agency has visibility into the entire development portfolio. Furthermore, the National Biodefense MCM Portfolio has significant gaps, even in programs for the highest priority threats. A planning model has been suggested for determining: the number of candidates concurrently investigated in order to yield a successful product within the desired timeline; the likelihood all desired products will be developed; the cost to support the complete portfolio; the number of candidates basic research labs need to supply to clinical development to keep advance development viable; and, how many products can be developed at one time.

A Portfolio advisory committee reviews and analyzes portfolio probability of success, gaps, and funding needs, and assist in interagency portfolio integration. A full inventory of MCM programs, DoD and civilian portfolios will be reviewed against stated requirements for identifying product strategies for each threat, with the plan that gaps and redundancies will subsequently be identified.

A gap analysis was conducted by the Defense Threat Reduction Agency - Chemical and Biological Technologies (DTRA-CB), the Joint Requirements Office (JRO), and JPEO to identify areas where research is not being conducted to address mission requirements. A knowledge gap in the areas of emerging and genetically-modified biological threats was identified and remedial actions taken in the form of launching the Transformational Medical Technologies Initiative (TMTI) to investigate these areas and provide subsequent data and products.

A similar need was identified in the Quadrennial Defense Review Report (QDR). Specifically, broad-spectrum medical countermeasures to defend against genetically engineered or naturally mutating pathogens, for which there are no current defenses, were identified in the report as needed capabilities for adequately defending the Nation and mitigating the consequences of attacks. The QDR identified two fundamental imperatives for the DoD: a continuation of the process to reorient the Department's capabilities and forces to be more flexible and adaptable to meet demands during wartime, in order to prepare for wider asymmetric challenges and to hedge against uncertainty over the coming years; and to implement enterprise-wide changes in order to ensure that organizational structures, processes, and procedures effectively support its strategic direction. In addition, the QDR stated the Department must also adopt a model of continuous change and reassessment if it is to defeat highly adaptive adversaries which are highly likely to pose asymmetric threats, including irregular, catastrophic, and disruptive challenges.

DHHS and DoD have also discussed the level of investment supporting the national portfolio for biodefense medical countermeasures during Fiscal Year 2004-2008 (FY04-FY08). As a result, a course of action was identified to harmonize technology readiness level frameworks into a language that promotes effective communication and interoperability, and a draft strategic decision criteria and measures of success were initiated.

The Task Force believes that while this is a clear step forward, more thought needs to be given to being explicit about what this effort can and cannot achieve, since the priority for the DoD is the prevention of morbidity and mortality due to bioterrorism, while the main mission for the DHHS is providing treatment after a bioevent involving the general population.

Briefs from the Services were also received by the Task Force regarding their research foci. Air Force biodefense is primarily devoted to counterproliferation and passive defense and consequence management, specifically, environmental and installation protection with a focus on decontamination, identification, assessment, and neutralization of air-borne threats. Key components of this research are devising kill mechanisms and disrupting the threat agent's ability to reproduce. The Task Force would like to emphasize that the need for an Air Force biodefense capability has been cited in multiple strategic documents; specifically tools are needed to locate, identify, track, assess, neutralize, destroy, and attribute threats in order to insure that Air Force operations are informed by research tailored specifically to the Air Force mission.

The Naval Medical Research Center and Biological Defense and Research Directorate (BDRD) biodefense research portfolio includes vaccines, molecular diagnostics, genomics, and immunodiagnostics. The Navy has a representative database that develops rapid reagents using antibody assays which are translated back to vaccines and examined in animal models.

The historical emphasis at USAMRIID has been on vaccines, while recent emphasis has been on therapeutics, with a focus on screening lead candidates and evaluation of efficacy in animals. The Diagnostics Systems Division at USAMRIID has only existed since 1995; the emphasis in recent years has been to provide support for the Joint Biological Agent Identification and Detection System (JBAIDS). Additional work has been done to develop immunoassays, with an emphasis on electrochemiluminescence (ECL) to support future field assay needs. In addition, USAMRIID supports the Joint Program Executive Office for Chemical Biological Defense's (JPEO-CBD) Critical Reagents Program (CRP), where it maintains and expands the DoD Unified Culture Collection (UCC) and where immunoassay reagents are developed and provided. Furthermore, USAMRIID is a participating member of the CDC Laboratory Response Network (LRN), and serves as a backup to the CDC for biocontainment facilities.

Effectiveness of Current Processes in Transferring Basic Research Results to Advanced Product Development and Licensure

The Task Force recognizes the identification of biologic candidates and their subsequent progression through the S&T and advanced development stages is an arduous, expensive, and protracted process. As such, clearly-identified priorities, strategies, coordination, and evaluation are necessary to ensure the efficient and successful transition of a product from discovery through licensing. While the basic research portfolio appears sound, it is challenging for the Task Force to submit a response with regard to the effectiveness of basic research transfer to advanced product development with the data it has been provided to date; however, the Task Force has identified several barriers toward advanced product development and licensure.

Organizational Structure, Management, and Oversight

Chemical and biodefense research within the DoD are guided by the JRO, with oversight by the Joint Service Office (JSO) and JPO. The Task Force made several observations based on the hierarchical and organizational schematics provided. Foremost, the organizational structure for biodefense research within the DoD constitutes a barrier toward advanced product development. Not only is the structure complex, unwieldy, and fragmented, it also strays from an industry best-practices model. A well-defined organizational structure, greater centralization, and transparency are needed to rectify the deficiencies in the DoD biodefense product acquisition process.

In addition, the Task Force noted a lack of the level of communication that is optimal between responsible entities, including the Service laboratories, resulting in duplicative research efforts and suboptimal use of available resources. Greater collaboration is needed, since biodefense research should be a joint effort; however, the Task Force recognizes a potential

challenge in the misalignment of the academic research timeline with military requests for product development. The Task Force believes the Integrated National Portfolio is a promising foundation for such efforts for the future.

Furthermore, a lack of one-person accountability and senior leadership with vaccine development expertise and experience serves as a barrier towards advanced product development. This is exacerbated by the following: frequent rotation of active duty members, different accountabilities and reporting authorities at various transition points throughout the lifecycle of product development, as well as a loss of intellectual capital due to difficulties inherent in transitioning competent and skilled junior-level military personnel to higher level leadership positions and retaining qualified scientists. Furthermore, the Task Force found that a true reporting hierarchy is needed, since little or no accountability with regards to an identifiable leadership currently exists, although oversight of the Chemical Biological Defense Program (CBDP) is provided by DTRA; however, the management and oversight issues the Task Force identified are complex and serve as a barrier towards advanced product development.

Efficiency and Effectiveness of Licensure Process for Investigational New Drugs (INDs)

The Task Force recognizes several challenges regarding product licensure impacting the efficiency and effectiveness of the licensure process for investigational new drugs (INDs), including regulatory requirements, overcoming research bottlenecks, and implications of FDA's "animal rule." Pharmaceutical drug discovery and development is lengthy and expensive, taking an estimated eight to twelve years and up to $1.2B to bring one drug to FDA licensure. The substantial increase in costs over time for pharmaceutical product development are due to FDA regulatory demands, increasing costs of research equipment, clinical trial size and complexity, and patient recruitment and retention in clinical trials. These factors are exacerbated by the limited commercial market for most biodefense pharmaceuticals. In light of these complexities, the Task Force encourages collaborations with academia and with other federal agencies in these endeavors. In addition, Congress must guarantee adequate funding to ensure continuation of projects through to licensure.

The DoD acquisition process is tailored to accommodate FDA regulatory procedures, which drive the cost, schedule, and performance regarding product development. All DoD Chemical Biological Radiological & Nuclear (CBRN) Defense Program medical products must be FDA approved; such authorizations are recognized as a Key Performance Parameter (KPP), while regulatory compliance is a core competency of Chemical Biological and Medical Systems (CBMS). CBMS utilizes government and commercial best practices to acquire FDA-approved CBRN medical countermeasures and diagnostics.

The FDA "animal rule" allows for the approval of vaccines in which efficacy testing in humans is unethical, and applies only when the agent's mechanism of action is reasonably understood, and where the product prevents disease or lessens effects of disease. Efficacy must be demonstrated in more than one well-defined animal model, where the study endpoints are related to product outcome in humans. As a result, well-controlled animal studies should yield

data likely to predict a benefit in humans. However, various complications arise in satisfying the requirements of the animal rule.

The animal rule imposes various constraints on research and ultimately supports few product candidates per year. As a result, compliance with the animal rule may impact readiness levels. The Task Force recognizes that increased clarity within DoD is needed with respect to compliance with the animal rule, and the misconception that animal rule approvals are a "shortcut." Challenges of developing biologics utilizing the animal rule include: increased costs as well as the requirement for additional data and the development of an appropriate animal model. The Task Force would like to emphasize that the infrastructure needed for animal testing is a significant constraint on biodefense MCM development, since a fact-based assessment of both "supply" and projected "demand" for animals and BSL 3 and BSL 4 facilities are necessary, and a proactive coordination procedure may be needed to meet program timelines.

Programmatic Processes and Evaluation

Within the CBDP, DTRA-CB is responsible for the management of the basic science portfolio of the DoD's biodefense program. The CBDP partnership consists of the JRO for Chemical, Biological, Radiologic, and Nuclear (CBRN) Defense, DTRA-CB and the JPEO-CBD. The JPEO is the executive agent for advanced development for Service-wide research pertaining to chemical and biological advancement; the JRO, JPEO, and Joint Science and Technology Office (JSTO) are involved in transferability. At the programmatic level an interagency committee, an Integrated Process Team (IPT), provides broad oversight and evaluates research proposals. The Military Infectious Disease Research Program (MIDRP) reviews research plans every three years facilitated by an American Institute of Biological Sciences (AIBS) Scientific Peer Advisory and Review Services (SPARS) panel, which assesses program goals and research proposals, and strives to ensure that research is balanced and meets the needs of the military.

JRO provides guidance with regards to biodefense research through establishing prioritized requirements based on data provided by the intelligence community, the combatant commands and Service representatives. Based on this input, the JRO provides an expansive list of research areas which are prioritized, discussed, and funded by the S&T sector and JPEO. The requirements from JRO are then conveyed to DTRA, then delegated to the Science and Technology (S&T) level where they are managed by DTRA-CB, incorporating processes from the DoD's acquisition model and FDA's regulatory requirements. The JPEO manages products as they emerge from S&T and transition to advanced development, beginning at the IND stage (Milestone A). The triad (DTRA-CB, JRO, and JPEO) meet on a quarterly basis, ideally to confirm that programs are aligned, transitions are planned, and best practices are employed to address any gaps. The Service laboratories are viewed as an integral component in the creation of possible solutions for the warfighter.

The solicitation process from DTRA is competitive and requires a bifurcated two-phase review of scientific and programmatic review. Solicitations include a description of purpose,

eligibility, Phase I and Phase II proposal submission requirements, evaluation criteria, a milestone schedule, points of contact and topics solicited. The criteria used in Phase I Pre-Proposal evaluations are Scientific and Technical Merit, and value to the Joint Chemical and CBDP Goals. Subject Matter Expert (SME) and CBDP stakeholder input is used to guide DTRA/Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD) invitations for Phase II Proposals. Phase II Proposals, consisting of an abstract, statement of work (SOW), a technical proposal detailing preliminary data, experimental design, personnel qualifications, facility capability and technical risk, a detailed cost estimate, and a project chart ("quad chart"), which lays out the project milestones, funding and obligation plan, expenditures, and status, are reviewed based on the following criteria: Scientific and Technical Merit; Value to Joint CBDP Goals; Technical Risk Facilities; Key Personnel Qualification; and Cost Realism. The Army Research Office (ARO) selects SMEs to evaluate each proposal in detail and provide a numerical or adjectival score, resulting in a merit order list. SME comments are used to guide funding decisions. The subsequent list is provided to a Selection Evaluation Board composed of CBDP stakeholders, who may accept or modify program plans. These decisions are then presented to the Selection Authority, the JSTO-CBD Director, for a final decision. The Director is the final authority for chemical and biological program funding decisions.

Upon reviewing the programmatic and evaluation processes, the Task Force observed the following: the systemic focus is on inputs, such as personnel and funding, rather than outputs in the process of transferring research findings to a licensed product; systematic evaluation metrics to evaluate programs are not evident; the ability to terminate projects is not apparent; and the level of external scientific review and input is unclear. The Task Force felt strongly that external programmatic review of biodefense research is necessary to identify gaps and provide the best scientific input. The Task Force would also like to emphasize previous findings that while its infrastructure is state-of-the-art and its workforce highly skilled, the chains of authority for the DoD process of pharmaceutical development is unnecessarily complicated and lacks oversight and balanced management (Martinez 2007).

Funding and Project Sustainability

Funding for biodefense medical countermeasures is distributed among many agencies, including: the National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA) within DHHS, the Defense Advanced Research Projects Agency (DARPA), CBDP and CBDP – Transformational Medical Technology Initiative (TMTI) within DoD. During the Contract Negotiation/Resource Reconciliation phase of program build, the budget and SOW is negotiated to optimize chemical and biological program research investment. FY10/11 DTRA JSTO-CBD funding decisions are briefed to the Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Program in the Office of the Assistant to the Secretary of Defense Nuclear and Chemical and Biological Defense Programs in the context of the planned FY10/11 investment strategy. DTRA allocates funds by task areas and not by product candidates; the DTRA-CB Directorate, JSTO, is tasked with funding and managing S&T up to IND submission, or

Milestone A. The projected funding for FY09 solely for pre-treatment (not therapeutics) is $25.42 M, the lowest since FY04.

Funding decisions are subject to change pending the outcome of the review. Final funding decisions consider scientific merit, programmatic priority, past performance, program balance, and fund availability. Awards begin only when the President's Budget is signed and funds become available. Multi-year funding is therefore subject to fund availability and adequate demonstration of progress toward program objectives. Quarterly reviews identify redundancies in research and are similarly dual-phased. In the event of duplication or failure of satisfactory project progress, DTRA and S&T are responsible for redirection and reallocation of funds.

The BDRD lacks core Navy funding, attains funds on a competitive basis, and retains the capacity for reimbursement. The main source of funds comes from DTRA; however, other funding streams originate from Fleet Support, JPEO-CBMS, as well as DTRA contracts from equipment and supplies.

Air Force funding focuses upon investigation of the attributes of the threat agent and less upon protective measures; consequently, it is important for the Air Force to maintain an independent research element. Several funding mechanisms exist, including external funds, or competitive awards and direct customer requests to address Air Force-specific needs or Joint needs through JSTO-CBD, as well as mixed funding targeting specific programs. If DoD is unable to provide funding, the Air Force utilizes its internal core funds to address their unique concerns.

Upon receiving briefs and reviewing data pertaining to funding, the Task Force made the following observations:

1. Separate lines of funding from different entities are not amenable to long-term project sustainability and success.

2. An adequate funding process must be ensured. Funding for licensed biodefense biologics will not be fully supported by the industrial sector and must come from the DoD. Therefore, a thorough evaluation should be conducted concerning realistic endpoints in regards to FDA licensure for the specialized vaccines that DoD needs to have available and for which the private sector does not require or support. Since it is neither feasible nor realistic to have adequate funding to license many such products, the U.S. government including the FDA and DoD, need to reevaluate the endpoints of the vaccine program as a major policy question. Defining the endpoints to be more realistic is critical.

3. The current funding system is arcane, since projects move at different speeds and problems exist with fund allocation. The Task Force is concerned about the possibility that DoD labs which would normally not acquire funding because of poor performance in academia or industry may be funded for decades in the military.

Transformational Medical Technologies Initiative (TMTI)

The Task Force received briefings regarding TMTI, which is focused on emerging threats and therapeutics, particularly countermeasures aimed at hemorrhagic viruses and intercellular bacteria. Its innovative "one drug, many bugs" approach is to develop broad-spectrum countermeasures and ultimately transform DoD's ability to protect against threats, since the traditional, commercial drug development strategy, "one drug, one bug" is neither flexible nor responsive to unknown pathogens or diseases, including advanced threats such as genetically engineered pathogens, or *de novo* viruses. TMTI also pursues novel medical countermeasures that target common disease pathways or enhance the immune system, while integrating the best efforts within government, academia, the DoD biotechnology industry, and pharmaceutical corporations.

Its business approach consists of multiple short- and long-term projects in the pipeline with the objective of providing seamless "end- to-end" product development, with numerous drug candidates in the near-term, while exercising rigorous milestone-driven program management that redirects funding to accelerate promising candidates in the pipeline.

Within the first two years, TMTI efforts have: initiated a robust portfolio containing 20 potential INDs and 12 platform technologies which build a rapid response capacity; submitted two pre-INDs to the FDA, leading to the first medical countermeasures against Ebola and Marburg hemorrhagic fever viruses; developed a genetic sequencing prototype capable of identifying pathogenic and genetically modified bacteria, transforming a process that previously required days into hours; created a genetic sequence database of biothreat agents, providing the capability to rapidly identify modified pathogens; and, implemented a platform for the rapid evaluation of promising therapeutic candidates and re-purposing of FDA-approved drugs. In addition, TMTI is characterized by active interagency participation and funds 36 projects from innovative biotechnology firms, pharmaceutical corporations, and academic institutions, most of who have previously worked with DoD.

The Task Force concurs that this approach is a highly innovative attempt at determining whether the industry model of management is practical in the realm of biodefense product research and development within the DoD. In addition, the Task Force recognizes that TMTI has a role in facilitating interagency cooperation and development. Effective execution of TMTI has aided in the transition of products to IND status, the origination of sequencing capabilities, and core platform development. Based on the findings outlined above, the Task Force believes TMTI is a novel experiment, and a potential management model that can be generalized to streamline the process of product submission, although some concerns were expressed as to whether TMTI has the ability to ensure competition or scientifically evaluate proposals thoroughly.

Scientific or Strategic Return on Investment (ROI) of Current Infrastructure

The Task Force recognizes the difficulties inherent in projecting the total cost for carrying a new pharmaceutical product from Research and Development (R&D) into production and marketing because each product has its own unique factors. It has been stated that the total cost for bringing a new drug to market has been estimated to be between $800M - $1B and requires approximately 10-15 years.

For the purposes of this interim report, the Task Force has defined return on investment to focus specifically on biologic biowarfare products to include diagnostics and vaccines utilized by service members, and not materials such as personal protective equipment and pharmaceuticals. To fully address this question would entail a detailed cost-benefit analysis. Since this could not be executable given the timeline of this investigation, the Task Force would like to present its insights resulting from a preliminary investigation and subsequent deliberation and suggestions for future perspectives for the purposes of this interim report. Details regarding the information from briefings received by the Task Force are outlined below.

The DTRA-CB effectiveness in managing the DoD CBDP S&T is evident in the transition of products for advanced development to JPEO to include: an Orthopox Antiviral Drug, the Joint Biological Agent Identification and Diagnostic System (JBAIDS), a Ricin vaccine, Plague vaccine, Hemorrhagic Fever vaccine, TMTI-sequencing platform anthrax diagnostic test and subunit vaccine, plasma and recombinant bioscavanger, and multi-valent Alphavirus vaccines. Outcomes from CBDP are uniquely warfighter-focused and include medical and non-medical countermeasures, critical information, and response capabilities. Medical countermeasures to CBDP-focused agents are of critical DoD and national security importance. However, there is often little commercial interest in the development of these countermeasures. Of the medical countermeasures, DTRA-CB focuses on areas related to pre-treatments, therapeutics, and diagnostics. Among the DTRA-CB funded programs, 114 patents were filed and 62 patents issued from Fiscal Year 1999 (FY99) to present. In addition, there are 45 Cooperative Research and Development Agreements (CRADAs) presently on file. Among transitioned products (pre-1990 to the present), there are 19 INDs; five INDs which transitioned to advanced development; four INDs which transferred to interagency partners; and three INDs which transferred to industry. CBMS successes from FY2000 to present include seven FDA approvals for biological defense medical products, 12 Investigational New Drugs (INDs), and two enabling technologies.

The value of Army expertise and infrastructure is apparent in the development of a myriad of diagnostic, vaccine, and therapeutic drug candidates to protect against biological threats such as: Smallpox, Anthrax, Tularemia, Botulinum neurotoxins, Hemorrhagic fevers, and Plague. On average, at least one new medical countermeasure is developed annually by Army scientists. Various critical reagents, such as antibodies for immunoassays, have transitioned from DoD laboratories to the JPEO-CBD Critical Reagent Program. Furthermore, Army biological aerosol sampling technology led to the establishment of the Portal Shield system, a fixed-site system used at airbases, ports, and Army bases in South Korea and South West Asia,

which in turn formed the technological basis of subsequent Homeland Security systems, such as Biowatch.

Two Army laboratories have earned national and international acclaim for their respective research efforts in medical chemical (U.S. Army Medical Research Institute of Chemical Defense) and biological defense research (USAMRIID), and were deemed "Centers of Excellence" by the National Institutes of Health. Both Army research laboratories are recognized for their premiere scientific and technology base, which enables a successful, highly synergistic partnership with industry. The Army possesses the largest collection of BSL 4 laboratories and the largest animal containment care facility in the U.S. In addition, the unique USAMRIID Center for Aerobiology is the sole research laboratory for the investigation of aerosolized biological warfare agents. Increasingly regarded as an essential partner in other federal agencies as well as industry and academia, USAMRIID investigators have developed numerous biological product candidates (mostly IND vaccines) and have engaged in animal studies, aerosol diagnostics, and *in vitro* studies. Since 2001, USAMRIID has been increasingly successful in securing licenses for its inventions. In addition, there has been a significant increase in Cooperative Research and Development Agreements (CRADAs) and intergovernmental agreements with NIAID, other federal government agencies, as well as industry and academia, since DoD laboratories are severely challenged to maintain a sufficient and incredibly diverse technical capability. Most of these collaborators are funded by a sponsor from either the DoD or DHHS, and customer demand is primarily focused on access to facilities for animal studies, diagnostic, and *in vitro* testing. As such, USAMRIID provides critical capabilities and a unique contribution to efforts undertaken in collaboration with industry, academia, and other federal agencies.

Between FY07-and FY08, there were 1432 active agreements, of which 354 were new agreements and included 85 CRADAs, in addition to Military Training Agreements (MTAs), Educational Partnership Agreements (EPAs), Cooperative Test Agreements (CTAs), and intergovernmental agreements. In the last five years, there were 3989 total active agreements, of which 1238 were new, and included 465 CRADAs. Additionally, 37 new U.S. patents and 16 new licenses were issued in the past five years, of which 12 patents and 7 licenses were issued in the past year. Currently, 350 Enzyme-Linked Immunosorbent Assays (ELISAs), 48 Electrochemiluminescence Assays, 45 (deoxyribonucelic acid) DNA assays, and 39 ribonucleic acid (RNA) assays are available and in various stages of development.

While WRAIR is a Center of Excellence for Infectious Disease Research, it is a relatively minor contributor in biodefense research; the past five fiscal years have been demarcated by four patents and two patents pending. No central office is responsible for processes related to return on investment.

The BDRD research portfolio includes vaccine-related research (new vaccine delivery systems, delivery of DNA based vaccines and therapies, human monoclonal antibodies, and innate immune agonists); molecular diagnostics (including recombinant reagents, assay development, reagent production, test and evaluation); genomics (developing capability to

rapidly characterize genomes of newly discovered potential biothreat agents); and immunodiagnositics, in order to develop and deploy rapid reagents and methods for the detection of non-nucleic acid biological molecules. Selected accomplishments include 34 CRADAs (12 between 1998-2003 and 22 in the last five years), one license (in 2001) and 31 patents (11 between 198-2003 and 19 in the last five years), the development of assays and reagents for 30 biothreat agents; the receipt of the 2005 Federal Laboratory Consortium (FLC) Award for Excellence in Technology Transfer; participation as a National Laboratory in the CDC's Laboratory Response Network (LRN); conducting large sample analysis for Federal agencies, including the analysis of 16,000 samples during the Anthrax event in 2001; deployment of two Mobile Laboratories for Operation Iraqi Freedom (OIF); and installation and maintenance of biowarfare detection capability on 26 ships. The accomplishments of the Infectious Disease Directorate includes immunodetection and quantitative polymerase chain reaction (qPCR) assays. Between 1992-1998, 33 assay products were delivered, while between 1998-2003, 89 assays and 150 antibody lot products against 18 biowarfare agents were supplied. In the past five years, 61 assays and 97 antibody lot products against 30 biowarfare agents were provided.

Past and future cost savings estimates regarding BDRD antibody production are significant. The Navy plays an integral role in the production of commercial assays. Within one year, BDRD produced antibodies (valued at $50M by the Critical Reagent Program) for under $2M, in contrast to the commercial price of $250M the industry would charge. If this figure were extrapolated over ten years, an estimated savings exceeding $2B would occur if BDRD rather than industry produced antibodies. Additional stockpiled plasma will save the DoD $12B in future antibody production. With regard to polymerase chain reaction (PCR) assay development, the total cost for outfitting ships with detection assays for ten agents was $8M, and is maintained for $800K per year. The estimated savings were totaled to be $65M. In addition, two million PCR reactions are produced for the DoD at a cost of $3 per reaction, for a total of $6M. The commercial price is approximately $10 per reaction totaling $20M, a net savings of $14M over 10 years to DoD.

Based on an initial review, the Task Force recognized several objective markers of considerable ROI, but felt that no systematic evaluation metrics, processes, or procedures were evident within DoD to evaluate programs. In addition, with the transition from a goal to "develop products to the IND state" to "develop FDA-licensed products," the personnel, processes, expectations, and progress required are unclear. The Task Force believes further effort should be expanded into the measurement, tracking, and evaluation of programs, processes, and procedures in place in order to optimize efficiency and maximize ROI. These include the establishment of well-defined metrics; the monitoring and tracking of results over time; the methodical reporting of results; and, a well-defined mechanism to eliminate non-productive programs.

CONCLUSIONS

The benefits of the DoD biodefense laboratories extends beyond the warfighter to impact national defense and the ability to promptly respond to bioterrorist events. While basic science

research is sound, barriers toward advanced product development and licensure exist, and affect both the efficacy and efficiency of a successful system that results in product development, and a successful effective maintenance of capabilities to respond to current and future biological threats.

RECOMMENDATIONS

In addition to the findings detailed above, the Board recommends:

1. **The DoD biodefense infrastructure should be retained. Further attempts should be made to create a national integrated biodefense campus in order to ensure accountability, enhance stronger leadership, and reduce costs and redundancies.**

2. **Medical countermeasures should be made a priority within the Department, and effective, synergistic collaborations established and incentivized to optimize the use of available resources and specific highly-developed expertise in the private and academic sectors. In particular, collaborations involving federal agencies, academia, and industry should be further developed, incentivized, and accelerated.**

3. **An adequate funding process to include realistic time lines and multi-year funding agreements must be ensured to meet the demands and challenges of the regulatory process.**

4. **Due to the significant financial investment and magnitude of people affected, DoD biodefense research programs should be tightly-focused and state-of-the-art, with transparent and well-defined priorities, timelines, and accountabilities, and a clear and timely ROI to both the service member and the Nation.**

5. **In the presence of rapidly changing threats, the biodefense programs should be flexible and able to realign given swiftly changing priorities and a lack of commercial interest.**

6. **Biodefense research program planning within the Department should be centralized and "joint" to optimize the long-term success in developing and deploying novel biodefense products.**

7. **DoD biodefense research priorities should be made explicit and transparent.**

8. **External scientific review and input need to be expanded and amplified.**

9. **Systematic scientific progress and ROI metrics to evaluate programs and terminate biodefense research projects should be established or made evident.**

10. **It is critical that sustained and identifiable performance accountability be implemented and efforts pursued to ensure leadership and work force capabilities.**

11. **Mechanisms to provide education and training for future DoD biodefense scientific leadership must be established.**

12. **Recruitment and retention of personnel with appropriate experience and expertise are essential to maintaining a sound infrastructure capable of efficient product development.**

13. **TMTI is a novel experiment, and its results should be evaluated and if successful, generalized throughout DoD.**

14. **To ensure appropriate efforts regarding biosurety, an authorized red team should be charged with defining and exploiting vulnerabilities.**

15. **Given the restricted time frame within which this Task Force developed these initial recommendations, the Board recommends the DHB Task Force further engage in a more comprehensive overall evaluation of the DoD biodefense infrastructure and biological research portfolio.**

Our observation is of highly dedicated, hard-working scientists and administrators determined to make a difference – but in the context of a major change of mission to developing FDA approved products – who are now failed by a slow system that tolerates complexity, lack of clear priorities, inadequate accountability, redundancy, inadequate funding, and lack of experienced leadership.

The Board gratefully acknowledges the significant contributions and efforts of the Army, Navy, Air Force, DTRA, JPEO, and the Office of the Special Assistant for Chemical & Biological Defense and Chemical Demilitarization representatives, and in particular LCDR Franca Jones in facilitating the review, providing background information, and offering insights into the complexities surrounding the DoD biodefense infrastructure and biological research portfolio. The Board would also like to recognize the participation and contributions of its members and consultants who participated in the Task Force and deliberated in this review.

The above conclusions were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:

Gail Wilensky, PhD
DHB President

Gregory A. Poland, MD
DHB Task Force Chair