OPTIMIZING INDUSTRIAL INVOLVEMENT WITH MEDICAL COUNTERMEASURE DEVELOPMENT:

A REPORT OF THE NATIONAL BIODEFENSE SCIENCE BOARD

February 2010

Optimizing Industrial Involvement with Medical Countermeasure Development (MCM): A Report of the National Biodefense Science Board (NBSB)

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Executive Summary – Under Development

Our Nation needs effective defenses against CBRN threats that could strike us without notice. These needs are the same needs as they were decades ago. It is time for the U.S. Government to better define its priorities, refine its focus, and accelerate the pace of MCM development.

Recommendations to the U.S. Government

1. **To harness the national industrial base, the U.S. Congress and the Executive Branch must provide adequate, consistent funding.**
2. **The U.S. Government must accelerate the pace of MCM development.**
3. **The U.S. Government must centralize its leadership for MCM development and acquisition, and optimize distribution methods.**
4. **The U.S. Government must demonstrate long-term commitment to its industry collaborators.**
5. **The U.S. Government must create, sustain, and enhance innovative partnerships with private industry.**
6. **The U.S. Government should expand MCM markets to include state and local first-responders and allied governments.**
7. **The U.S. Government must do a better job of preparing for anticipatable emergencies.**
8. **Various departments and agencies of the U.S. Government must act in concert to ensure success.**

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Overview

The Need for Medical Countermeasures

America needs safe and effective defenses against chemical, biological, radiological, and nuclear (CBRN) threats that could strike without notice. These needs have persisted for decades with too little progress toward developing a comprehensive and readily available cache of medical countermeasures (MCM),[1] including drugs, vaccines, and diagnostics. Now is the time for the U.S. Government to "pedal faster," to provide leadership, innovate, and accelerate the pace of MCM development. Such efforts will have direct benefits in strengthening national security. Indirect benefits will accrue by advancing the biomedical sciences and enhancing our international competitiveness. This report pinpoints specific actions for the U.S. Government (the U.S. Congress and components of the Executive Branch) to take to protect the American people against CBRN threats. Individual States cannot take responsibility for protecting their residents until the Federal Government provides the tools—in the form of MCM—to do so.

The development of MCM against CBRN agents is a critical national security issue. To meet its requirements for MCM, America needs leaders who will build collaborations between government and industry. The inherent complexity of drug and vaccine development requires time and persistence. Drug discovery and development cannot be "surged" in any meaningful way, especially for CBRN incidents that could happen without notice. In contrast to the development of drugs and vaccines against influenza,[2] there are inadequate market forces or other incentives to sustain a vibrant, responsive, and flexible industrial base for CBRN MCM without substantial government investment and path-clearing. A sustained and adequately resourced national effort must address a broad spectrum of threats. Inconsistent and inadequate funding for CBRN MCM development over the last several decades is simply incompatible with the potential consequences of these threats.

Recent years have seen important advances by the U.S. Government in improving the environment for MCM development. The creation of the Biomedical Advanced Research and

[1] Medical countermeasures include qualified countermeasures as defined in section 319F–1(a) of Public Health Service Act (42 U.S.C. section 247d–6a(a)); qualified pandemic or epidemic products per section 319F–3 of Public Health Service Act (42 U.S.C. section 247d–6d)), and security countermeasures per section 319F-2(c)(1)(B) of Public Health Service Act (42 U.S.C. section 247d–6b).

[2] The M&S-WG focused on MCM to defend against the malicious release of CBRN agents, rather than naturally occurring diseases such as pandemic influenza. Because a multibillion dollar and growing market for influenza countermeasures (e.g., vaccines, antivirals, therapeutic agents, diagnostics) already exists, and improvements can often harness existing technologies, the barriers and incentives to the development of influenza MCM are vastly different and are not considered in this report.

Development Authority (BARDA); the option for an Emergency Use Authorization (EUA);[3] rules of evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or feasible (i.e., the "animal rule"); the recent agreement between the U.S. Department of Health and Human Services (HHS) and the U.S. Department of Defense (DoD) for an "Integrated Portfolio" approach to MCM development;[4] and the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) stakeholder meetings and workshops, among others, are welcome improvements.

Nonetheless, progress in developing CBRN countermeasures has been too slow, and many pathogen targets need to be countered.[5] A particularly difficult challenge, which does not exist in routine drug development, is to create MCM solutions for unrecognized or genetically modified pathogens. Also, the transitions from basic research to advanced product development, to procurement and stockpiling, and ultimately to deployment are not adequately coordinated. The President's Homeland Security Presidential Directive (HSPD)-18 appropriately cites the need for an integrated approach to CBRN MCM development that draws upon the expertise of the public health, life science, defense, homeland security, intelligence, first-responder, and law enforcement communities, as well as the private sector, to promote a seamless integration through the various stages of MCM product development.

The legacy of MCM development dates back to the 1950s, and even earlier. Various combinations of public and private effort have been tried (e.g., federal laboratories, direct contracts, prime-system contractors), with limited success in terms of products licensed or approved by the Food & Drug Administration (FDA) (See Table 1). The DoD has been actively researching and developing multiple drugs and vaccines for decades.[6] The 2001 anthrax attacks focused attention on the need to accelerate the development of MCM against CBRN agents to protect civilians as well as military personnel. Yet the last eight years have seen only limited progress toward national goals. Admittedly, the development pipeline for new drugs, vaccines, and diagnostics is long, convoluted, and costly, sometimes stretching 10 to 20 years or longer.[7]

[3] Under section 564 of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3), as amended by the Project Bioshield Act of 2004 (Public Law 108-276), the FDA Commissioner may allow medical countermeasures to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by such agents, when there are no adequate, approved and available alternatives. For details, see www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm.

[4] Portfolio Advisory Committee (PAC) Charter, the "Integrated National Biodefense Medical Countermeasures Portfolio" (Integrated Portfolio), January 6, 2010. See https://www.medicalcountermeasures.gov/BARDA/RandD/RandD.aspx.

[5] "HHS Public Health Emergency Medical Countermeasure Enterprise Implementation Plan for Chemical, Biological, Radiological, and Nuclear Threats," Washington, DC: U.S. Department of Health and Human Services; April 2007. (See Tables 2 and 3) Available at www.hhs.gov/aspr/barda/phemce/enterprise/strategy/index.html.

[6] Institute of Medicine. "Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military." Washington, DC: National Academy of Sciences, 2002; and Institute of Medicine. Giving Full Measure to Countermeasures: Addressing Problems in the DoD Program to Develop Medical Countermeasures Against Biological Warfare Agents. Washington, DC: National Academy of Sciences, 2004.

[7] Matheny J, Mair M, Mulcahy A, Smith BT. Incentives for biodefense countermeasure development. *Biosecur Bioterror* 2007;5(Sep):228-38; Munos B. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews* 2009;8959-68; and Barrett ADT, Beasley DWC. Development pathway for biodefense vaccines. *Vaccine* 2009;27:D2-D7.

But the inventory of promising candidate MCM in the latter stages of development is modest at best.

Today's list of needed CBRN MCM is considerably longer than the list of licensed MCM currently stocked in the Strategic National Stockpile (SNS).[8] One addition to the SNS is the current smallpox vaccine, which is produced with a more modern manufacturing process than the vaccine it replaced. Several unlicensed MCM are now available in large quantities that could be deployed under an EUA (e.g., anthrax antitoxins and botulism antitoxin). Large quantities of antibiotics and other supplies also have been stockpiled.

More needs to be done.
National security interests make it the responsibility of the U.S. Government to do more, faster, to provide for our biological defenses.

Table 1 summarizes the current status of existing and needed MCM according to their regulatory and SNS status. It is important to note that not all threats (i.e., the rows in Table 1) are equally consequential, thus each MCM (i.e., each annotated cell) is not equally important for national security. Further complicating MCM development is that various MCM fall along a spectrum of scientific feasibility. For example, the production of safe and effective MCM against typhus and glanders is a relatively lesser technical and programmatic challenge than the development of filovirus vaccines (i.e., for Ebola and Marburg viruses). HHS and DoD are taking the appropriate steps to prioritize and time-phase MCM development, based on threat assessments and the state of the science for each MCM.

[8] "HHS Public Health Emergency Medical Countermeasure Enterprise Strategy for Chemical, Biological, Radiological, and Nuclear Threats," Washington, DC: U.S. Department of Health and Human Services; March 2007.

Table 1: Top-Priority MCM[9] Against Chemical, Biological, Radiological, and Nuclear Threats, Annotated by License and Stockpile Status, Reflecting HHS and DoD Programs, February 2010

	Vaccine	Antitoxin	Antibiotic or Antiviral Agent(s)	Antidotes and Related Agents	Acute & Delayed Effects of Radiation	Nuclide-Binding Agents	Diagnostics	Biodosimetry, Bioassay
Anthrax	A, SNS	H, SNS	A, B, SNS				A JBAIDS	
Botulism	D	A, H, SNS					✦	
Filoviruses (Ebola, Marburg)	D		✦				✦	
Glanders, Melioidosis			✦				✦	
Junin virus			✦				✦	
Plague	D		A, B, SNS				✦ JBAIDS	
Smallpox	A, H SNS		B, SNS, ✦	A (VIG), SNS			✦	
Tularemia			A, B, SNS				✦ JBAIDS	
Typhus			✦				✦	
Radiological-nuclear threats					B, SNS, ✦	A, SNS		✦
Volatile nerve agents				✦ Chem-pack				

A – MCM is licensed or approved by the FDA for this use.
B – Product is licensed or approved for other uses; eligible for use as MCM under EUA.
D – Candidate MCM in DoD program is not yet licensed by FDA.
H – Candidate MCM in HHS program is not yet licensed by FDA.
Chempack – Packages of atropine, pralidoxime, and diazepam.
JBAIDS – DoD's Joint Biological Agent Identification and Diagnostic System.
SNS – MCM is stocked by the Strategic National Stockpile.
VIG – Vaccinia immune globulin.
✦ – Designates MCM that are neither licensed by FDA nor stocked by SNS, but are national priorities and being pursued by HHS.

[9] Adapted from Table 2 in "HHS PHEMCE Implementation Plan for CBRN Threats"; April 2007; available at www.hhs.gov/aspr/barda/phemce/enterprise/strategy/index.html; and the "Project BioShield Annual Report to Congress": August 2007 through December 2008, available at www.hhs.gov/aspr/barda/bioshield/annualreport/index.html.

Questions about MCM Innovation, Markets, and Sustainability

One of the persistent questions in discussions about national policy (i.e., legislation, regulation, and implementation) has been how best to engage the private sector in the development of MCM. After all, most biopharmaceutical innovation has come from the private sector where most industrial-scale development and production expertise resides. Private-sector industry, in this case, is a heterogeneous mixture of large and small pharmaceutical companies, large and small biotechnology companies, and a wide array of supportive companies with expertise in delivery devices, formulation, assays, contract manufacture, contract research, and many other relevant activities.

To review issues of MCM development in depth, the National Biodefense Science Board (NBSB), established two working groups at its inaugural meeting. The NBSB is a Federal Advisory Committee established in December 2006 by the Pandemic and All-Hazards Preparedness Act (PAHPA).[10] The Board provides expert advice and guidance to the Secretary of HHS on scientific, technical and other matters regarding current and future chemical, biological, nuclear, and radiological agents, whether naturally occurring, accidental, or deliberate, as well as other matters related to public health emergency preparedness and response.

The NBSB charged the MCM Research & Development Working Group with reviewing the intertwined portfolio of activities within HHS and DoD, evaluating effective interagency collaborations, identifying gaps and redundancies in the federal research portfolios, and making recommendations to enhance innovation, research, and the development of medical countermeasures. The NBSB charged the Medical Countermeasure (MCM) Markets and Sustainability Working Group (M&S-WG) with several goals:

- Review existing financial, policy, and regulatory issues that influence industry willingness to invest in the development of vaccines and therapeutic products for use as MCM.
- Identify real and perceived barriers-to-entry that have affected industry participation in the development of MCM.
- Identify incentives that could encourage industry partners that are currently reluctant to engage in MCM development.
- Inform NBSB discussions and recommendations regarding the development of sustainable markets for MCM and how to encourage investment by the private sector in the development, manufacturing, and distribution of MCM.

In an April 16, 2009, letter, the Assistant Secretary for Preparedness & Response stated "BARDA and its partners … request the Board's continuing input on identifying and achieving the ways and means needed to develop and sustain fuller engagement by the biotechnology and pharmaceutical industries to support our vital national security mission. …"

[10] U.S. Public Law 109-417, codified at Title 42 U.S.C. sections 219a and 247d-7f; 120 Stat. 2831 (2006). See www.hhs.gov/aspr/nbsb.

NBSB Working Group Inventory of Industry Constraints and Incentives

During its fact-gathering phase with targeted telephone interviews, the M&S-WG repeatedly heard MCM development efforts in the United States referred to as fragmented, with confusing approaches at multiple points. To bring order to the complexities of MCM development, the M&S-WG assembled an inventory of factors that could discourage industry involvement or partnering with the U.S. Government, reported constraints to industry involvement, and potential solutions for relief from particular constraints.

The M&S-WG published its "Inventory of Issues Constraining or Enabling Industrial Involvement with Medical Countermeasure Development" and called for public comment in August 2009.[11] Based on this and other feedback, the WG strengthened and refined the inventory, which is provided in Appendix 1. Next, the WG drafted a set of recommendations for the U.S. Government to consider as it strengthens the Nation's biodefenses. The full NBSB subsequently considered the efforts of both working groups,[12] and adopted the content and recommendations embodied in this report.

The inventory is categorized into broad themes of financial, legislative, scientific, human capital, regulatory, and societal elements. Individual entries are placed according to their dominant themes. It brings perceived problems and proposed solutions together into one matrix, to assist policy makers. The barriers and constraints have not been prioritized, scored, or priced. It is important to note that the inventory includes some proposals and potential solutions that are not commonly accepted. Indeed, various commentators agreed or disagreed with various combinations of these solutions. Also, the two-dimensional structure of the inventory does not fully resolve some overlap among these categories, especially with regard to regulatory issues.

Among the public comments on the inventory was a recommendation to place more emphasis on developing broad-spectrum MCM that avoid the resource-intensive nature of a one-bug/one-drug approach. Although broad-spectrum MCM offer advantages, their probability of successful development is uncertain. Some investment in broad-spectrum MCM is appropriate, but the current emphasis on targeted MCM remains prudent, to provide a balanced portfolio.

Findings of the NBSB Markets & Sustainability Working Group

Assessment of the MCM Enterprise and its Stakeholders

The PHEMCE leads HHS efforts to develop and acquire MCM that will improve public health emergency preparedness, as well as prevent and mitigate the adverse health consequences associated with CBRN and naturally occurring threats. The PHEMCE is a coordinated, intra-agency effort led by the Office of the Assistant Secretary for Preparedness and Response (ASPR)

[11] Department of Health and Human Services. The National Biodefense Science Board (NBSB), a Federal Advisory Committee to the Secretary; Request for Public Comment. *Federal Register* 2009;74(153–Aug 11):40189-99.
[12] "Report of the NBSB Medical Countermeasure Research and Development Processes for Chemical, Biological, Radiological, and Nuclear (CBRN) Agents," November 18, 2008.

and includes three HHS agencies: the Centers for Disease Control and Prevention (CDC), the FDA, and the National Institutes of Health (NIH). Additionally, the PHEMCE collaborates with its *ex officio* members: the DoD, the Department of Homeland Security (DHS), the Department of Veterans Affairs (VA), and other interagency stakeholders, as appropriate.

HHS recognizes that multiple stakeholders play key roles in MCM development, procurement, and deployment. These stakeholders include other Federal departments and agencies; private industry (domestic and international); State, local, and tribal governments; first responders and healthcare workers; academia; and the public.

DHS issues Material Threat Determinations (MTD) for those CBRN agents that pose a material threat to national security,[13] by integrating findings of the intelligence and law enforcement communities with input from the scientific, medical, and public health communities. DHS also issues material threat assessments (MTAs), to define plausible, high-consequence scenarios that include estimates of the number of people who would be exposed to the threat agent. In response, the PHEMCE has issued requirements for what kind and how much of specific MCM the nation needs under various use conditions. These requirements are determined by several factors, including threat assessments defining various agent-release scenarios, medical and public health consequence modeling, MCM utilization scenarios, MCM role (e.g., in pre-exposure prophylaxis, post-exposure prophylaxis, presumptive treatment, or definitive treatment), the number of people affected, and the characteristics of the MCM that form a target product profile (TPP, i.e., desired indications, formulations, dosing, delivery mechanisms, packaging, storage and transport, shelf life, or other considerations focused not just on stockpiling but on the end user's needs).[14]

The NBSB encourages the U.S. Government to consider two types of project-management scenarios for MCM development:

- Routine development of desired MCM (along the lines of routine pharmaceutical/biotech development), as well as
- Scenarios for which no MCM is available and a program where timelines must be drastically compressed if lives are to be saved.

The H1N1 pandemic of 2009−2010 bears some characteristics of the second scenario, but the pandemic developed after several years of preparatory effort had already occurred and could be prevented or treated with MCM that were similar to existing vaccines and antiviral drugs. To date, the 2009−2010 pandemic involved a virus of relatively low pathogenicity (compared with other influenza pandemics, such as that of 1918). Had the influenza strain been resistant to stockpiled antiviral drugs, delays in vaccine production could have resulted in a much greater disease burden.

[13] Material Threat Determinations (MTD) are authorized under section 319 F-2(c)(2) of the Public Health Service Act, as added by section 3 of the Project BioShield Act and are a legally required precursor to procurements under that authority. 42 U.S.C. § 247d-6b; see also www.hhs.gov/aspr/barda/requirements..

[14] BARDA. For more information about the process of "Requirements Setting" for MCM development and acquisition, see www.hhs.gov/aspr/barda/requirements/index.html.

Had the 2009−2010 influenza pandemic instead involved an unexpected release of tularemia, plague, or a genetically modified pathogen, America would have found itself more vulnerable, because MCM against these agents are still in early stages of development. Serious gaps in MCM preparedness still exist, and the pace of shoring up the nation's medical defenses remains unacceptably slow.

Private-sector representatives with relevant experience who were interviewed for this project perceive a lengthy process to generate requirements. These representatives consider contracting with the U.S. Government to be slow, unwieldy, expensive and opaque. Lack of clarity about MCM requirements, potential procurement size, warm-base requirements, length of regulatory review, and reliability of sustained funding increases industry risk and reduces willingness to participate. Additional questions arise regarding the contract-review process and rate of issuance of new proposals. This becomes even more critical when consortia of companies are needed to fully develop any given MCM.

Once a contract with the U.S. Government is in place, the situation improves, according to private-sector representatives. HHS is viewed as cooperative, helpful, responsible and responsive. Nonetheless, a perceived lack of coordination among Federal agencies with MCM development activities and regulatory responsibilities remains a concern to industry. For example, there is a lack of clarity regarding the earliest point at which a product may be usable, a status essential for compensating developers under several BioShield-funded contracts. Common understanding of what constitutes a "usable product" has not been established. Indeed, products could be usable under a variety of mechanisms, including emergency Investigational New Drug (IND) status, standard IND protocols, and EUAs. Further, there appear to be differences in approaches between the FDA's Center for Biologics Evaluation & Research (CBER) and Center for Drug Evaluation & Research (CDER) in terms of providing guidance to industry. Unlike most commercial situations, the MCM industry must rely on the U.S. Government for key components of regulatory submissions (e.g., disease studies, toxicology reports, access to facilities that may use select agents and toxins, and access to biosafety level-4 facilities), which can require extensive government-industry coordination and prioritization.[15]

Considering the needs of civilians and military personnel for safe and effective MCM, the White House and its Homeland Security Council, DoD, and HHS have identified common goals as well as requirements specific to each Federal entity, and are using taxpayer dollars for research efficiently. The Integrated Portfolio for developing CBRN MCM is a good first step, but will need substantial effort by both Departments to achieve their respective goals in the most efficient and effective manner possible.

MCM markets are relatively immature. Most of the efforts needed to make them viable will require making the markets broader and more sustainable. Sustainment includes preserving manufacturing capacity after initial lots of an MCM have been produced, sometimes referred to as maintaining a "warm base" for subsequent manufacturing of supplies to replace initial quantities that reach the end of their expected shelf life. Planning for warm-base aspects of sustained production, as well as product life-cycle management and the incessant progress of

[15] National Research Council. "Overcoming Challenges to Develop Countermeasures Against Aerosolized Bioterrorism Agents: Appropriate Use of Animal Models". Washington, DC: National Academy of Sciences, 2006.

biotechnology need to be considered from the early stages of development and acquisition. The sustainment of MCM markets requires a specific funding stream.

Historical Comparison of MCM Development with Other National Industrial Efforts

MCM development requires unprecedented cooperation and integration across the U.S. Government, industry, and academia. To develop nuclear weapons in the 1940s, the U.S. Government funded and/or operated most of the laboratories. The Manhattan Project was a widely dispersed, multi-component, cutting-edge science and engineering project to develop the first nuclear weapons. "Manhattan Project" has become an iconic name applied to other massive efforts to develop new technologies. The real Manhattan Project took three years (1942 to 1945) to achieve its main goals.

The pace of MCM development against CBRN threats does not compare well to the real Manhattan Project. Part of this comparison is unfair, insofar as the Manhattan Project had a single goal, whereas the MCM enterprise has multiple sub-projects involving the remarkable complexity of human biology. But unlike the focused effort of the 1940s, it is apparent that the U.S. Government has not committed adequate resources for MCM development, and is insufficiently resolved to accomplish the important goals described in HSPD-18, Medical Countermeasures Against Weapons of Mass Destruction.[16]

The situation for MCM development might be more like that faced by the U.S. Navy or the National Aeronautics & Space Administration (NASA). To build aircraft carriers in the 1930s, the Navy set specifications, and for-profit shipyards built the ships. Additional orders over the intervening decades have permitted those ship builders to attract and retain talented workers. The steady pace of acquisition of new aircraft carriers gives the private sector confidence that the U.S. Congress and Executive Branch are likely to continue acquisition at a predictable rate.

In the 1960s, NASA contracted with the commercial aerospace sector for lift vehicles and spacecraft. America's space program benefited from innovative contracting authorities (e.g., Other Transaction Authority, OTA) to enable greater collaboration than typically is permitted by the Federal Acquisition Regulations (FAR).[17] But "boom" and "bust" cycles since the 1960s led to the loss of uniquely trained workers, and slowed the pace of space exploration. MCM developers also have experienced boom and bust cycles, where starts and stops in congressional appropriations and White House support led to the lay-off of scarce scientific and engineering talent.

One of the outstanding questions for the biopharmaceutical industry is whether the U.S. Congress will appropriate adequate funding, sustained across a decade or two, for MCM discovery, development, trials, and licensure of the full MCM portfolio. The aerospace industry knows today that future military aircraft will be funded at some reasonably predictable rate,

[16] HSPD-18, "Medical Countermeasures Against Weapons of Mass Destruction," January 31, 2007. www.fas.org/irp/offdocs/nspd/hspd-18.html.
[17] Halchin LE. "Other Transaction (OT) Authority," Congressional Research Service, Report No. RL34760, November 25, 2008.

based on historic patterns established the 1950s. But the biopharmaceutical industry cannot point to such a precedent. Consider the 10-year Special Reserve Fund of $5.6 billion authorized by the Project BioShield Act in 2004.[18] In FY 2009, $412 million of this reserve was diverted to fund MCM for pandemic influenza or for advanced research and development.[19] Further, in FY 2010, more than $600 million was diverted from Project BioShield—$305 million to fund advanced research and development within BARDA, and another $304 million to the National Institute of Allergy and Infectious Diseases (NIAID).[20] Setting aside the merits of other funding targets, repeated diversions of the Special Reserve Fund raise doubts about the intentions of multiple sessions of the U.S. Congress to consistently fund the MCM enterprise. Because the available funds for advanced MCM development are so short, and the process of advanced development[21] must precede procurement, there may be merit in such a transfer within BARDA's own accounts. But transfers must be avoided, if industry confidence in the U.S. Government as a partner is to be fostered.

A modified approach to MCM development might be worth considering. Analogous to the DoD Congressionally Directed Medical Research Programs[22] that were developed to bridge the prerogatives and processes of multiple federal institutions, a modified approach could be tested. Because MCM development against CBRN is a national security issue, a White House representative could form and chair an MCM integrated product team and monitor its progress. Team members could include experts from the Federal Government, industry, academia, and other civilian entities. The group could work under a waiver granted by the USG (such as a variant of Federal Advisory Committee Act requirements) that would allow national experts in the field to contribute to a process of identifying requirements and critical criteria needed for a drug, vaccine or diagnostic. This waiver would permit them to compete under standard Federal Acquisition Regulation (FAR) conditions for requests for proposal (RFPs) that would be released based on their work. This is an unusual method, but could attract the most-informed advice available. For each Government-established and -prioritized requirement, this team would review the maturity of the relevant science, the urgency of end-user needs, and appropriate funding levels. The findings of the team group (e.g., scientific gaps, industrial shortfalls, potential problems with critical path, points of risk of failure) would then be passed to Government leadership, to determine which Federal agency(ies) would be responsible for each phase of development and acquisition for that MCM. The leadership could bring this team together on a periodic basis to assess progress toward goals, based on parameters such as cost, schedule and performance. This approach assumes that the U.S. Congress continues to fund

[18] The Project BioShield Act of 2004 (P.L. 108-276) is available at, http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ276.108.pdf.
[19] Omnibus Appropriations Act, 2009 (PL 111-8). Gottron F. Project BioShield: Purpose and Authorities, Congressional Research Service, Report No. RS21507, July 6, 2009.
[20] "Budget strips more than $600 million from BioShield program." *Global Security Newswire*, January 8, 2010.
[21] There is no commonly accepted definition for which point of development qualifies as the last step of early development or the first step of advanced development. The Pandemic and All-Hazards Preparedness Act (P.L.109-417) definition of *advanced research and development* is "activities that predominantly are conducted after basic research and preclinical development of the product; and are related to manufacturing the product on a commercial scale and in a form that satisfies the regulatory requirements under the Federal Food, Drug, and Cosmetic Act or under section 351 of this Act."
[22] For information about the DoD Congressionally Directed Medical Research Programs, see http://cdmrp.army.mil/default.htm.

multiple agencies to develop MCM. An alternative suggestion is to designate one Federal agency responsible for MCM development based on prioritized civilian and DoD-unique requirements and fund that agency adequately. That agency could adopt the process outlined above. Obviously, these approaches need additional detail and discussion.

Approach to Developing MCM against Radiological and Nuclear Threats

Although most of the efforts of the two NBSB Working Groups were spent considering biological MCM, the working groups also considered the processes in place to develop MCM against radiological and nuclear threats. Like their MCM against biological threats, MCM against radiological and nuclear threats are also highly dependent on animal-model research and specific criteria for establishing safety and efficacy. Unfortunately, resources devoted to the development of MCM against radiological and nuclear threats seem to be less adequate than those applied to biological threats.

To develop MCM for radiological and nuclear threats, a consortium based at the University of Maryland School of Medicine, the Medical Countermeasures Against Radiological Threats (MCART), was established in April 2005. The prime focus of the MCART consortium is the development of MCM to treat the major sub-syndromes and organ injury of acute radiation syndrome (ARS), and the delayed effects of acute radiation exposure (DEARE). Treatments for these conditions include MCM that bind to and then remove inhaled or ingested radionuclides from the body.

The MCART consortium consists of 14 components and an organizational structure capable of developing MCM suitable for the Strategic National Stockpile. The consortium includes six research sites (three universities, two nonclinical contract research organizations, and one institute); a statistical design and data analysis core; two manufacturing sites; two clinical trial centers (supporting phase 1 safety trials); and three companies with expertise in information technology, regulatory affairs, quality assurance, good laboratory practice (GLP), and data and document management. Oversight of MCART activities is provided by the NIAID Radiation Countermeasures Research and Preparedness Directorate.

The development of radiological-nuclear MCM is highly dependent on establishing an animal-model research platform for ARS/DEARE in two or more animal species. The MCART consortium has developed multiple animal models to integrate murine and nonhuman primate (NHP) data, minimize confounding variables, and propose means of medical management in humans. Each treatment protocol is considered in the context of a target product profile for humans who have been exposed to potentially lethal doses of radiation. MCART consortium members have reported that conducting GLP-compliant experiments in animal models while also adhering to data-management principles under compliant processes with validated equipment is particularly challenging.

Hematopoietic and gastrointestinal radiation exposure syndromes are areas were HHS and DoD are effectively working together on MCM. The Integrated Portfolio for CBRN MCM exhibits a

growing trend throughout the U.S. Government to avoid redundancy. Another example of DoD and HHS collaboration is the development of MCM against chemical agents.

Evaluation of the Current Situation

The principal barriers hindering industrial involvement of MCM against CBRN include: (a) inadequate and inconsistent funding; (b) opportunity costs (e.g., distractions from other industrial missions); (c) economics (e.g., financial margins and low volumes); (d) uncertain regulatory pathways; (e) finite human capital; (f) the complexity of working with multiple federal agencies; (g) inadequate Federal Government understanding of the commercial biopharmaceutical enterprise; and (h) the use of an acquisition system created to procure complex mechanical equipment such as aircraft, vehicles, and ships.

The principal incentives to encourage industrial involvement could include: (a) financial incentives (e.g., grants, tax credits, priority review, and long-term contracts); (b) access to a larger pool of scientists and engineers; and (c) preferred access to new intellectual property.

To date, however, the incentives to private industry to develop MCM against CBRN agents have not been sufficient to overcome the real and perceived barriers cited in this report. Logically, a mixture of reducing the barriers and enhancing the incentives would be needed to harness the full national industrial capacity to expeditiously generate and field CBRN MCM.

The U.S. Government cannot create an effective MCM program without an unusually close degree of interaction and collaboration with industry. This relationship was forged over the years with aerospace and maritime industries, but has yet to occur with biotechnology and pharmaceuticals.

Recommendations to the U.S. Government

1. **To harness the national industrial base, the U.S. Congress and the Executive Branch must provide adequate, consistent funding.** MCM development is expensive, resource-intensive, and time-consuming, with a high level of risk. Drugs and vaccines for national biodefense have little, if any, commercial market. Several groups have proposed recommendations for federal funding levels to ensure advanced development of MCM.[23]

[23] For recommendations on federal funding levels for advanced MCM development, see the following examples of reports:

- Commission on the Prevention of WMD Proliferation and Terrorism. "Prevention of WMD Proliferation and Terrorism Report Card," available at http://www.preventwmd.gov/prevention_of_wmd_proliferation_and_terrorism_report_card/.
- "Task Force for America's Health. Ready or Not? Protecting the Public's Health from Diseases, Disasters, and Bioterorism, 2009." Available at http://healthyamericans.org/reports/bioterror09/pdf/TFAHReadyorNot200906.pdf.
- Cooperative Agreement Research Study between Defense Advanced Research Projects Agency (DARPA) and University of Pittsburgh Medical Center (UPMC), Jul 2007-Mar 2009. "Ensuring biologics advanced development and manufacturing capability for the United States Government: A summary of key findings and

Additional federal funds likely will be needed for MCM development and acquisition.. Inadequate funding delays and derails the journey to MCM licensure; the negative impact of inconsistent funding is even more severe.

A. Advanced Development: The U.S. Congress and Executive Branch should provide increased dedicated funding for advanced MCM development, which is distinct from procurement funds. Because most CBRN MCM are in early stages of development, more resources for advanced development will be needed before procurement funds ar required. The 10-year Special Reserve Fund for Project BioSheild remains a procurement device, not an advanced-development mechanism. But no MCM will be available to be procured, unless advanced development succeeds first.

B. Procurement: The BioShield Special Reserve Fund expires in 2013 and needs to be reauthorized and fully funded. These funds should not be diverted to support other initiatives, regardless of the merit of the other purposes. Congress should consider giving BARDA authority to reprogram 10 to 40 percent of its funds on an annual basis, to advance MCM candidates through the pipeline as efficiently as possible. The need for other improvements in BARDA's functions and authority should also be explored.

2. **The U.S. Government must accelerate the pace of MCM development and acquisition, and optimize distribution methods.** MCM discovery and development are matters of national security and, as such, are distinguished from routine research and development activities. National vulnerability does not end when a project is funded, but rather when MCM are stockpiled and licensed, and an effective distribution process is in place to distribute them quickly.

3. **The U.S. Government must centralize its leadership for MCM development, procurement, and approval.** Strong, coordinated leadership is important if private-sector entities are expected to risk their capital to develop MCM against CBRN. This leadership, perhaps coordinated at the level of the White House or through a specified Federal agency, is needed to synchronize, prioritize, integrate, and coordinate all essential MCM development activities across Federal agencies, industry, and other relevant stakeholders, including not-for-profit organizations.

4. **The U.S. Government must demonstrate long-term commitment to its industry collaborators.** MCM development requires unprecedented cooperation and integration across the U.S. Government and industry. Multiyear funding with carry-over authority and multiyear contracting authority would signal durable U.S. Government commitment and increase industry's sense of long-term stability. Drug development is a complex, long-term process. Multiyear contracting authority is essential to allow long-term planning and

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conclusions" is available at http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=ADA506569.

- Matheny J, Mair M, Smith B. Cost/success projections for U.S. biodefense countermeasure development. *Nature Biotechnol* 2009;26:981-3.
- Klotz LC, Pearson A. BARDA's budget. *Nature Biotechnol* 2009;27(Aug):698-9 (letter).
- Matheny J, Mair M, Smith B. BARDA's budget: Reply. *Nature Biotechnol* 2009;26:699 (letter).

eliminate uncertainty about the availability of federal funds. One-year budget cycles for Federal agencies (DoD is the notable exception) constrain the ability of private industry to plan coherently or execute MCM development effectively. Programs should be tied to specific national security goals and subjected to regular progress assessments. A new approach to acquisition that departs from the equipment-procurement model is essential, while also ensuring financial propriety, maintenance of competition, and achievement of goals and timelines.

5. **The U.S. Government must create, sustain, and enhance innovative partnerships with private industry.** Advanced-development projects should be commissioned with innovative contracting mechanisms, such as OTAs, and other flexible means. Cost-plus-fee contracting flexibility is appropriate for advanced development and would reduce industry risk. The U.S. Government could explore the formation of task-organized consortia or similar assemblies of industrial talent, so the Government can request assistance from specific subsectors of the biopharmaceutical industry when problems arise. BARDA, FDA, and other U.S. Government agencies must be willing to innovate and take risks, so they fulfill the public trust to make safe and effective MCM available as soon as possible. Effective channels of communication among these entities also are essential.

6. **The U.S. Government should expand MCM markets to include state and local first-responders and allied governments.** These markets are relatively small, but including them would send industry an important message that the U.S. Government is not the only market.

7. **The U.S. Government must do a better job of preparing for anticipatable emergencies.** By their nature, CBRN attacks are unpredictable. But some scenarios can be anticipated and it is incumbent upon the U.S. Government to plan for them. Such scenarios include the potential exposure of children to anthrax spores; therefore, the U.S. Government should undertake clinical trials to determine the appropriate pediatric dose of anthrax vaccine. Similarly, several other MCM should be assessed for pediatric dosing. For CBRN incidents that arise before an MCM is licensed, that MCM may need to be administered in EUA status. Rather than wait until a CBRN incident occurs to assemble the scientific data needed by the FDA to issue an EUA, the U.S. Government should draft mockup pre-EUA dossiers and data sets for the unlicensed/unapproved MCM most likely to be needed. These preparatory activities would help establish the proper size of an MCM market and speed up distribution activities. Not to prepare in these ways runs the risk of wasting time and lives when attacks strike.

8. **Various departments and agencies of the U.S. Government must act in concert to ensure success.** The progression of candidate MCM products from basic research through advanced development to stockpiling and distribution must be as integrated and seamless as possible. Target profiles for needed MCM should be developed early in the development process, to avoid repeating early development steps and to streamline the progress of candidate products. FDA should enhance its processes for providing guidance to industry. The Integrated Portfolio approach recently adopted by HHS and DoD is promising, but will need sustained effort to make this concept a reality. HHS and DoD

must communicate sufficiently to support both their common interests and their unique requirements.

Conclusion

America needs safe and effective MCM against chemical, biological, radiological, and nuclear threats as much as it needs the Army, Navy, Marine Corps, Air Force, Coast Guard, and Public Health Service to provide for national security. Past combinations of public and private activity have not been sufficient to develop, procure, and field the MCM America needs for adequate biodefense.

In the past few years, the Project BioShield Act provided for a procurement fund to foster the development of medical products that did not yet exist. Although subsequent legislation attempted to target resources for the advanced development of MCM, this funding has never been adequate. Until the Federal Government creates efficient processes for the advanced development of MCM, it will not be able to procure these products.

It will be essential for national leaders, including the President, to insist on an innovative and relentless pursuit of the full portfolio of MCM. Multiple government agencies will need to find a way to overcome the status quo and accelerate the pace of MCM development.

With adequate resources and effective leadership, the various agencies of the U.S. Government can work together and harness the expertise of the private sector in ways similar to those used to produce aircraft carriers, land men on the Moon, and accomplish other "Manhattan Projects." This report focuses on identifying barriers and providing incentives for the private sector. To help ensure the success and sustainability of MCM development, it also includes recommendations for enhancing coordination and collaborations between and among HHS agencies (e.g., NIH, CDC, FDA, BARDA) and components of DoD.

It might be useful to consider MCM development to be more a matter of engineering (i.e., testing prototypes) than a matter of science. In other words, drug development involves an iterative, back-and-forth endeavor to test and refine alternatives that requires repeated consultation with those who set requirements, those who regulate, and those who develop. This brings us back again to the historic examples of aircraft carrier production and the NASA's development of technology for space exploration. "If we can put a man on the Moon, why can't we…?" is an iconic cry of frustration.

The direct value of fielding licensed MCM is to enhance national security. The indirect value will come in enhancing our competitiveness internationally and in learning what can be applied to other biopharmaceutical endeavors. Indeed, investments in MCM development have already

new yielded diagnostic systems for infectious diseases, with additional gains expected. Further benefits will accrue as this knowledge is applied to combating other infectious diseases and public health problems.

It will be essential for national leaders, including the President, to insist on an innovative and relentless pursuit of the full portfolio of MCM. Multiple government agencies will need to find a way to overcome the status quo and accelerate the pace of MCM development.

America's security depends on adding licensed CBRN medical countermeasures to its arsenal of defenses as soon as possible. Enemies will not issue advance warnings they are about to attack with CBRN weapons. Protecting the nation against CBRN threats relies on discipline, vigilance, perseverance, determination, and commitment.

Appendix 1.
Inventory of Issues Constraining or Enabling Industrial Involvement with Medical Countermeasure Development

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	FINANCIAL		
Capital requirements to establish safety, efficacy, validated manufacture	Increase financial return after risking capital to industry-standard rates Reduce requirement for private capital for advanced development	Increased federal funding for advanced development, in the form of cost-reimbursement contracts and rewarding private-capital investments with milestone payments and at procurement	Risk of distraction of large industry partners from commercial (and public health) mission. Risk of dilution of effort [potential conflict with fiduciary responsibility to shareholders of publicly-traded companies]
	Enhance current incremental R&D tax credit (increase, make refundable)	Currently, 20% for qualified R&D expenses and 50% for clinical-trial expenses	
	New investment tax credit (20%) for construction of new R&D and manufacturing facilities for biosecurity and emerging infectious disease purposes (with refundable and/or transferable provisions)	Enhance net revenue	
Risk of technical failure of vaccine development effort	Decentralized discovery / centralized development and manufacture	Reimbursement of development costs at cost + 15%, with return-on-working-capital at 22%, and cost-of-money-for-capital at 15%	Lack of interest, given opportunity costs Congressional tolerance for anticipatable frustrations is unknown
	Indirect-cost reimbursement greater than 100% Assistance with calculating indirect cost rates (for companies without experience)	Provides support early in development process.	
Revenue enhancements based on Intellectual Property	Enhance current product or use patent-term restoration and/or extension (revise formula) Allow full patent-term extension for licensed products that gain CBRN or emerging disease application (akin to adding pediatric indication).	Current statutory formula: Patent extension supplemented by [1/2 time from IND to filing BLA + full time from BLA filing to FDA approval/licensure]	

	Allow transfer of patent-term extension to another product or company ("wild card") Market exclusivity: Increase term of market exclusivity to ~ 12-15 years and extend it to biologicals (as does Orphan Drug Act).	Currently, 5 years of market exclusivity is provided to New Chemical Entities but not biologicals via Hatch-Waxman Act and 7 years of market exclusivity is provided via Orphan Drug Act.	"Wild card" approach may be problematic in terms of social equity. Note: Orphan drug tax credit applies to vaccines only if fewer than 200,000 recipients anticipated.
Priority-Review Vouchers (PRV)	Make applicable to biosecurity products.	A PRV is a tradable certificate awarded for a licensed treatment for a neglected tropical disease. It entitles holder to a priority review (a speedier review time) for a future product of its choosing, potentially shortening the review process by 6 to 12 months. First PRV awarded to Novartis for *Coartem* malaria treatment (artemether and lumefantrine) in April 2009.	Predictability: Would a priority-review voucher simply accelerate a "no" or "not yet" regulatory response? 2007 law: Text at: www.bvgh.org/documents/HR3580-CompromiseFDA-PDUFABill.pdf Draft FDA guidance: www.fda.gov/cber/gdlns/tropicaldisease.htm
Limited market size (development costs >> market potential)	Acquisition Requests for Proposal (RFPs) issued soon after MCM requirement established, stating minimum quantities (total and to each successful awardee) and other important details (e.g., packaging, storage, route of administration), to increase market certainty to potential bidders and their investors.	Timely publication of requirements along with advanced-development RFPs. Seek to more widely describe procurement requirements, in contrast to the more sensitive value of treatment requirements.	MCM requirements are not static and can be expected to change based on threat assessments and discoveries during product development.
	Contract terms allowing manufacturers access at market rates to allied foreign governments and other authorized customers outside the US, as well as civilian first responders, hospitals, and travel-vaccine providers within the US. DoD incorporates this practice to some degree.	Treaty allies represent additional markets, to enhance industrial sustainability and provide security support to allies.	Allies have not made substantial independent MCM purchases to date. Some allies may hope or expect USG to share stockpile after attack occurs. DoD has sold MCM to other governments at discounted prices that undercut private-sector sales.
	Add biodefense and other adult vaccines to Standardized Equipment List (SEL) and Authorized Equipment		Currently only drugs, antidotes, and various treatments are covered, but not vaccines for pre- and post-

	List (AEL), so state and local first-responders can use federal (DHS) grant funds to pay for vaccinations.		exposure prophylaxis.
Surge issues	Incentives for industry partners to develop expanded capabilities that can be used commercially during non-emergency times (analogous to Civil Reserve Air Fleet, CRAF). Compensation if commercial product(s) displaced during emergencies (e.g., lost sales, market share, delayed licensing).	Define "compensation" in initial contract or agree to a dispute-resolution mechanism.	Validated cleaning of sterile suites and restoration to commercial use could be troublesome technically and for public acceptability. Potential compensation may need to include delay of a new product or loss of market share to a competitor. Level difficult to determine *a priori*.

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	LEGISLATIVE		
Predictability, consistency, adequacy of Congressional appropriations	Increase [NIAID] appropriation for early-stage CBRN MCM development to offset flat funding since 2001 anthrax attacks. Insufficient funds now allocated. Increase [BARDA] appropriations for advanced development of CBRN MCM and continued long-term funding for procurement, to offset recent funding shortfalls. Insufficient funds now allocated. Need reauthorization and adequate funding of both advanced-development efforts and BioShield Special Reserve Fund. Increase DoD appropriations for advanced development and procurement of CBRN MCM. Insufficient funds now allocated.	Multi-year contracting authority (for large molecules, due to complex manufacturing and limited use) and multi-year funding with carry-over authority for R&D and procurement initiatives. Manage funding across departments and agencies as an "integrated portfolio" that mitigates risk by a broad set of target products, with multiple MCM per disease. Base metrics on portfolio performance, rather than individual candidate MCM. Long-term funding and ongoing government procurement (10 years or longer) essential to maintain warm-base MCM manufacturing and surge capacity (sustainability).	Limited track record. Partial analogies: Aerospace industry since early 1940s. Consistent appropriations for aircraft carriers since late 1930s. Congressional long-term recognition of threat (natural and malicious) and tolerance for MCM technical failure unknown.
Funding stream	Provide greater flexibility in milestone-driven payment schedules under PAHPA and BioShield, to account for the unpredictability of vaccine R&D technical difficulties and progress. Make greater use of non-traditional and non-procurement instruments, such as Other Transaction Agreements (OTAs) and Cooperative Agreements. Adopt a blend of indefinite mandatory funding authority with caveats to assure good-faith performance and sufficient ongoing discretionary appropriations.	PAHPA (2006) authorized $1B to BARDA for advanced development of MCM, in addition to BioShield Special Reserve Fund. OTAs could facilitate cooperative relationships and tailored contracts that balance Government needs and developer's concerns. OTAs suited to unpredictable technical difficulties inherent in R&D. Consider Commercial-Item contracting techniques, as provided in FAR Part 12 (48 CFR Part 12 et seq), to allow balance of risk and cost-effective methods to investigate development pathways.	

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	SCIENTIFIC		
Untrodden development pathways	Cooperative R&D Agreements (CRADAs) allow collaboration with respect for intellectual property. U.S. Gov't and sponsor agree on defined development pathway (e.g., basis for licensure, regulatory requirements) at early stages to achieve a target product profile.	Recognition that changes in product requirements are expected to increase cost and time required to achieve usable product. Requires enhanced integration of efforts by each USG entity (notably BARDA, NIAID, CDC, FDA, DoD, InterAgency Board for Equipment Standardization and Interoperability). Place nonproprietary data (e.g., natural history, animal model data) from federally funded MCM development efforts in public domain, or make available to MCM partners via electronic information-sharing technology.	
Facilitating technology transfer from basic to advanced development	Streamline process to support integration of disciplines needed for successful scale-up of manufacturing processes. Increase U.S. Gov't funding for applied bioscience, material sciences and biopharmaceutical processes. Increase U.S. Gov't investment in facilities and upgrades to comply with requirements for handling Biological Select Agents and Toxins (BSAT) and chemical agents.	Offer innovator an option of (a) a milestone payment ("prize") as a single fee to license the intellectual property for further development or (b) continue involvement in development in exchange for the possibility of royalties after FDA licensure achieved. Enhanced coordination and priority setting needed between NIAID and BARDA, to effectively span the spectrum from discovery to licensure, reflect end-user needs when filing Investigational New Drug (IND) applications, and minimize waste of resources. Document the transition process. U.S. Gov't could lease facilities to private sector. Revenue would support maintenance; industry would not need to invest in their own facilities.	Milestone payments could be used on a multiple of private paid-in capital (variable) or a fixed amount per drug.

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	HUMAN CAPITAL		
Human capital within industry	Expand the pool of science and engineering talent within industry needed to develop and manufacture MCM within the US.	Increased range of scientific programs offers additional career-development for industrial scientists and engineers. DARPA model assumes industry-standard compensation rates. Congress funded increases for NIH grants for researcher awards, but a long-term approach is needed to sustain the industrial base.	Additional flexibility needed in authority to provide competitive compensation to critical federal employees.

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	REGULATORY		
Complex, evolving regulatory requirements	Clarify expectations early in product development and minimize revisions during in application review (e.g., requirements under "animal rule," pre-EUA assessment of adequate data).	Spill-over benefits to commercial sphere via enhanced dialog with FDA.	FDA. New drug and biological drug products; evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or feasible. Final rule. *Fed Reg* 2002 May 31;67(105):37988-98.
	Implement best practices for quality/regulatory systems for biosecurity products	Partner with experienced biopharmaceutical organization to gain access to expertise and/or quality systems.	Companies with extensive regulatory experience not currently engaged with MCM development or manufacture.
	More collaboration between FDA and industry, to meet evolving stringent standards for development, manufacture, clinical trials, and "animal-rule" pathways.	Centralized advanced development and manufacturing to facilitate cross-product learning and system development.	
	Federal legislation to preempt state and local laws, regulations and court decisions that have requirements that differ from requirements imposed under the Federal Food, Drug and Cosmetics Act (FFD&C Act) and FDA regulations.		State and local government requirements for drugs, biologicals, and medical devices that conflict with FFD&C Act pose substantial burdens on MCM developers

	Accelerated FDA review		
Administrative requirements to comply with USG contracts	Contracting reform to relieve the regulatory and reporting burden. Enhance industry understanding of USG acquisition processes through training (e.g., online courses through Defense Acquisition University, www.dau.mil).	Waive nonessential accounting requirements and other components of the Federal Acquisition Regulation (FAR). BARDA increases use of Other Transaction Authority (OTA) for R&D contracts (akin to DARPA). Use Cooperative R&D Agreements (CRADAs).	Familiarity with Federal Acquisition Regulations (FAR) (or relief from them)
Adequacy of review and consultation resources at FDA	Increase FDA appropriations to enhance ability to perform timely review and provide additional consultation services.	More medical reviewers needed, plus research and assay development capability. Increase percentage of personnel eligible for enhanced bonus payments or super-grades. Assure sufficient FDA staff has appropriate security clearances.	

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	SOCIETAL		
Contribution to national security	Development of biosecurity MCM could have spill-over benefits to "natural" infectious diseases as well, such as bioprocess improvements that could have multiple applications.	National capacity to respond to biological threats would not only prevent casualties directly, but it may also help to serve indirectly as a deterrent against attack. Enhanced corporate reputation for partners.	Increased public attention during crisis

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	LEGAL		
Product liability	Expand and fund coverage of PREP Act to MCM for which Material Threat Assessments (MTAs) exist. Adequate funding authority needed for injury-compensation claims. Federal legislation to preempt state and local laws, regulations and court decisions that have requirements that differ from requirements imposed under the Federal Food, Drug and Cosmetics Act (FFD&C Act) and FDA regulations.	Indemnification via Public Readiness & Emergency Preparedness (PREP) Act of 2005 (PL 109-148, Dec 30, 2005)	PREP Act not tested in practice or litigated. The effect of the 2009 Supreme Court decision on preemption is uncertain. www.pandemicflu.gov/plan/federal/prep_act.html PL 109-148. PHS Act Section 319(f)(3). 42 USC § 247d-6d. [see also Support Antiterrorism by Fostering Effective Technologies (SAFE-T) Act of 2002 [within Homeland Security Act, PL 107-296].]
Antitrust Provisions	Assess and implement antitrust waiver authority under PAHPA 2006 for R&D and preparedness activities to allow nominally competing parties to collaborate during an emergency or to conduct contingency exercises before an emergency. Involve DoJ and Attorney General.	Need ability to develop contingency plans and conduct preliminary communication and technical consultation before an emergency develops. Continue and expand efforts such as those underway with pandemic influenza vaccine and adjuvant "mix-and-match" studies to assess safety and efficacy.	

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
	COROLLARY		
Attractiveness of commercial vaccine market for support of future R&D and manufacturing	Implement national policies to provide adequate reimbursement for vaccines and their administration in both the public and private sectors, to help underwrite and sustain the industrial base needed for biosecurity and global-health products	Consolidate Medicare coverage of all vaccines within Part B (not Part D). Increase administration reimbursement rates under Medicaid and Vaccines for Children (VFC) beneficiaries with federal subsidies to offset increased State costs. Third-party payers to provide first-dollar coverage for FDA-licensed vaccines and their administration under healthcare reform.	
Approaches suitable for developing-world situations (perhaps useful by analogy)	Advanced Market Commitments (AMC) separately for existing vaccines and global health vaccines at R&D stage	Examples: Guarantee a market in developing countries for pneumococcal vaccines to prevent deadly respiratory infections in children and as an incentive for development of vaccines that currently do not exist against infectious disease threats in those countries, but which may be imported into the U.S. or threaten global security.	
Competitive situation	Allow multiple technologies and product candidates to progress simultaneously through development pathways. DoD approach is competitive prototyping and teams.	In competitive environment, it may be desirable to make down-select decisions as late as possible, so as not to preclude innovation and deny the U.S. Gov't the insights of one of the developers.	
New intellectual property (IP)		IP developed in course of government contract remains with discoverer.	U.S. Gov't has step-in rights if patent arising from federal government-funded research not exploited [Bayh-Dole Act of 1980 (or University & Small Business Patent Procedures Act), codified in 35 USC § 200-212[1], implemented by 37 CFR 401[2]
Staying abreast of advancing science		Access to state-of-art process analytics for wide variety of biological products	Need to understand exclusivity of access

Appendix 2. Acronyms and Abbreviations

AEL - Authorized Equipment List
AMC - Advanced Market Commitments
ARS - Acute Radiation Syndrome
ASPR - Office of the Assistant Secretary for Preparedness and Response
BARDA - Biomedical Advanced Research and Development Authority
BLA - Biologics License Application
BSAT - Biological Select Agents and Toxins
CBER - Center for Biologics Evaluation and Research
CBRN - Chemical, Biological, Radiological, and Nuclear
CDC - Centers for Disease Control and Prevention
CDER - Center for Drug Evaluation and Research
CRADAs - Cooperative Research and Development Agreements
CRAF - Civil Reserve Air Fleet
DARPA - Defense Advanced Research Projects Agency
DEARE - Delayed Effects of Acute Radiation Exposure
DHS - Department of Homeland Security
DoD - U.S. Department of Defense
DoJ - Department of Justice
EUA - Emergency Use Authorization
FAR - Federal Acquisition Regulations
FDA - Food and Drug Administration
FFD&C Act - Federal Food, Drug and Cosmetics Act
GLP - Good Laboratory Practice
HHS - U.S. Department of Health and Human Services
HSPD - Homeland Security Presidential Directive
IND - Investigational New Drug
IP - Intellectual Property
JBAIDS - Joint Biological Agent Identification and Diagnostic System
M&S-WG - Markets and Sustainability Working Group
MCART - Medical Countermeasures Against Radiological Threats
MCM - Medical Countermeasures
MTA - Material Threat Assessments
MTD - Material Threat Determinations
NASA - National Aeronautics and Space Administration
NBSB - National Biodefense Science Board
NHP - Non Human Primate
NIAID - National Institute of Allergy and Infectious Diseases
NIH - National Institutes of Health
OTA - Other Transaction Authority
PAC - Portfolio Advisory Committee
PAHPA - Pandemic and All-Hazards Preparedness Act
PHEMCE - Public Health Emergency Medical Countermeasures Enterprise
P.L. – Public Law
PREP Act - Public Readiness & Emergency Preparedness Act
PRV - Priority-Review Vouchers
R&D - Research and Development
RFP - Request for Proposal

SAFE-T - Support Antiterrorism by Fostering Effective Technologies
SEL - Standardized Equipment List
SNS - Strategic National Stockpile
TPP - Target Product Profile
UPMC - University of Pittsburgh Medical Center
U.S.C. – United States Code
USG - United States Government
VA - Department of Veterans Affairs
VFC - Vaccines For Children
VIG - Vaccinia Immune Globulin
WG - Working Group
WMD - Weapons of Mass Destruction

Appendix 3. Roster for the NBSB MCM Markets & Sustainability Working Group

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