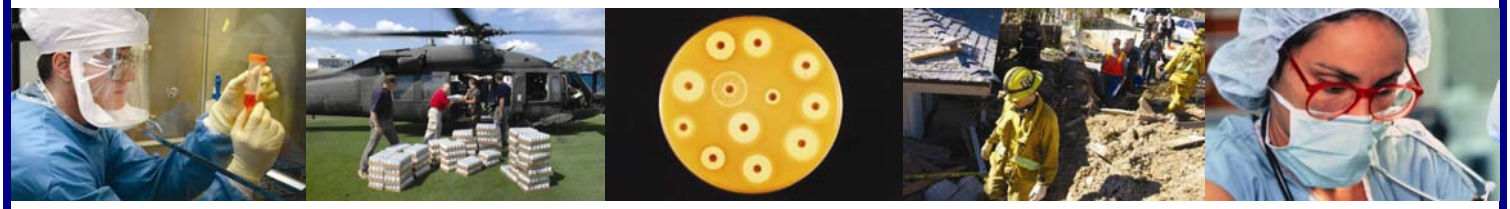
OPTIMIZING INDUSTRIAL INVOLVEMENT IN MEDICAL COUNTERMEASURE DEVELOPMENT:



A REPORT OF THE NATIONAL BIODEFENSE SCIENCE BOARD

February 2010

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

TABLE OF CONTENTS

Executive Summary

The development of medical countermeasures (MCMs) against chemical, biological, radiological, and nuclear (CBRN) threats is a critical national-security issue. The United States must develop, acquire, stockpile, and distribute safe and effective defenses against CBRN agents that could strike without notice. Today's needs for developing a comprehensive and readily available cache of MCMs—drugs, vaccines, diagnostics, and other products—fundamentally are the same needs as they have been for many years. It is time for the U.S. Government to define clear priorities, focus its efforts and resources on this national-security priority, and accelerate the pace of MCM development and acquisition. To be effective, a comprehensive MCM program will require an unusually close degree of interaction and collaboration between the U.S. Government and private industry.

Since the dissemination of *Bacillus anthracis* (anthrax) spores through the U.S. mail in 2001, the Federal Government has created a range of mechanisms to facilitate MCM development, acquisition, and use. These mechanisms include the creation of the Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services (HHS); the option for Emergency Use Authorizations (EUAs); rules of evidence needed to demonstrate the effectiveness of new drugs when human efficacy studies are not ethical or feasible (i.e., the "animal rule"); the recent agreement between the Department of Health and Human Services (HHS) and the U.S. Department of Defense (DoD) for an "Integrated Portfolio" approach to MCM development; and the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) stakeholder meetings and workshops, among others.

The Homeland Security Presidential Directive (HSPD)-18, issued in January 2007, appropriately cites the need for an integrated approach to MCM development "that draws on 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. However, despite substantial federal investment, our Nation still does not possess the arsenal of defenses it needs to protect itself from CBRN threats. Further, the unique needs of children for MCMs have not been afforded adequate attention or effort.

This report was prepared by the Markets and Sustainability Working Group (M&S-WG) of the National Biodefense Science Board (NBSB). It emphasizes the need to accelerate the development of MCMs to protect against biological threats—i.e., to "pedal faster"—although the NBSB recognizes that more efficient MCM development against nuclear and radiological weapons, as well as chemical weapons, also is necessary. The report summarizes the findings of the NBSB M&S-WG, which includes real and perceived barriers that have prevented effective industry participation in the development of MCMs. Finally, the report issues eight recommendations to the U.S. Government that, if implemented, should result in more persistent

and more innovative efforts to develop the full portfolio of MCMs needed to protect the country against CBRN agents.

The Need for Medical Countermeasures

The development of MCMs against CBRN agents is a critical national-security issue, but the list of MCMs needed to counter CBRN threats is considerably longer than the list of licensed MCMs currently in the Strategic National Stockpile (SNS) (see Table 1). Not all CBRN threats are equally consequential; HHS, DoD, and the U.S. Department of Homeland Security (DHS) have identified a list of top-priority agents for MCM development, acquisition, and placement in the SNS. One of the persistent questions in efforts to develop MCMs has been how best to engage the private sector.

In August 2009, the NBSB M&S-WG published an "Inventory of Issues Constraining or Enabling Industrial Involvement with Medical Countermeasure Development" in the *Federal Register*. Based on feedback from key stakeholders and the public, the Working Group refined the inventory, which is provided in Appendix 1 of this report. The inventory is organized into broad themes to reflect financial, legislative, scientific, human capital, regulatory, and societal issues. The goal of devising the inventory is to assist policymakers by bringing together perceived problems and proposed solutions for MCM development into one, comprehensive matrix.

Findings of the NBSB Markets and Sustainability Working Group

Unlike the Manhattan Project of the 1940s, or the effort to build lift vehicles and spacecraft for the National Aeronautics and Space Administration (NASA) in the 1960s, Government-industry collaborations to develop MCMs against CBRN threats have been hampered by real and perceived barriers. The following list indicates important barriers identified by the NBSB M&S Working Group.

- Federal funding for MCM development has been inconsistent and inadequate. The lack of reliable multiyear funding decreases the willingness and ability of industry to participate.
- Contracting with the U.S. Government is viewed by industry as being slow, unwieldy, expensive, and opaque. However, once a contract with the U.S. Government is in place, the situation improves, according to private-sector representatives.
- There is a lack of clarity from the U.S. Government about MCM requirements, potential procurement size, and the length of time needed for regulatory review.
- There is a perceived lack of coordination among Federal entities with MCM development activities and regulatory responsibilities.
- The complexity of working with multiple Federal entities impedes the process of MCM development.

- The need for highly trained individuals to work in private industry to develop MCMs is greater than the availability of essential human capital.
- There is an inadequate understanding of the commercial biopharmaceutical enterprise within the Federal Government.
- The system for MCM acquisition needs to be updated and refined. The current acquisition system was created to procure complex mechanical equipment such as aircraft, vehicles, and ships.
- The commercial market for MCMs is too immature and insufficient to function as an incentive to industry to develop these products.
- Insufficient mechanisms are in place to sustain industry involvement in MCM development by preserving manufacturing capacity after initial lots of an MCM have been produced.

The full NBSB subsequently considered the efforts of both working groups, and adopted the content and recommendations embodied in this report on February 10, 2010.

Recommendations to the U.S. Government

America's security depends on adding multiple, diverse, licensed MCMs against CBRN agents to its arsenal of defenses as soon as possible. Enemies of the United States will not issue advanced warning they are about to attack with CBRN weapons. It is therefore essential for national leaders to renew their focus and accelerate the development of safe and effective drugs, vaccines, and diagnostics required to counter top-priority CBRN threats. To achieve these goals, the Federal Government and private industry must work together. In addition, multiple Government entities must overcome the barriers that currently hinder the efficient development, acquisition, and stockpiling of MCMs needed.

To date, the Federal Government's incentives to private industry to develop MCMs against CBRN agents have not been sufficient to overcome the real and perceived barriers cited in this report. A combination of reducing the barriers and enhancing incentives is needed to harness the full national industrial capacity required to develop and field, as expeditiously as possible, safe and effective MCMs against CBRN threats. The principal incentives to encourage industrial involvement could include financial incentives such as grants, tax credits, priority review, and long-term contracts; access to a larger pool of highly trained scientists and engineers; and preferred access to new intellectual property.

The NBSB M&S-WG issues the following eight recommendations to the U.S. Government to reduce barriers and provide incentives to optimize industry involvement in the development of MCMs against CBRN threats for both adults and children.

Specific Recommendations:

1. To harness the national industrial base, the U.S. Congress and the Executive Branch must provide adequate, consistent funding. Medical countermeasure (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 MCMs. Additional federal funds likely will be needed for MCM development and acquisition. Inadequate funding delays achieving the goals of MCM licensure, stockpiling, and distribution; 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 funding. Because most MCMs against chemical-biological-radiological-nuclear (CBRN) agents are in early stages of development, more resources for advanced development will be needed before procurement funds are required. The 10-year Special Reserve Fund for Project BioShield remains a procurement device, not an advanced-development mechanism. But no MCMs will be available to be procured, unless advanced development succeeds first.

B. Procurement: The Project 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. The U.S. Congress should consider giving the U.S. Department of Health and Human Services' (HHS's) Biomedical Advanced Research and Development Authority (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 MCMs are stockpiled and licensed, and an effective distribution process is in place to distribute them quickly or in advance of an event.

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 MCMs against CBRN agents. This leadership, perhaps coordinated at the level of the White House or through a specified Federal entity, is needed to synchronize, prioritize, plan, integrate, and coordinate all essential MCM development activities across Federal entities, 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 eliminate uncertainty about the availability of federal funds. One-year budget cycles for Federal entities (the Department of Defense 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 MCM 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 Other Transaction Authority and other flexible means. Cost-plus-fee contracting flexibility is appropriate for advanced MCM development and would reduce industry risk. The U.S. Government could explore the formation of task-specific consortia or similar assemblies of industrial talent, so the Government can request assistance from specific subsectors of the biopharmaceutical industry when problems arise. BARDA, the Food and Drug Administration, and other U.S. Government entities must be willing to innovate and take risks, so they fulfill the public trust to make safe and effective MCMs 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 international partners, State, local, and tribal governments, laboratorians, and first-responders in each of these sectors. These markets are relatively small, but including them would send industry an important message that the U.S. Government is not the only market. Adding MCMs to Standardized Equipment Lists (SELs) and Authorized Equipment Lists (AELs) would allow State and local first-responders to use federal grant funds to protect these personnel against occupational hazards.

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 MCMs should be assessed for pediatric dosing. For CBRN incidents that arise before an MCM is licensed, that MCM may need to be administered under Emergency Use Authorization (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 more mockup pre-EUA dossiers and data sets for the unlicensed/unapproved MCMs 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 in the event of a CBRN attack.

8. Various departments, agencies, and entities 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 MCMs 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.

Optimizing Industrial Involvement in Medical Countermeasure Development:

A Report of the National Biodefense Science Board (NBSB)

February 2010

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 (MCMs),[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 MCMs—to do so.

The development of MCMs against CBRN agents is a critical national-security issue. To meet its requirements for MCMs, 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 occur without notice. In contrast to the development of drugs and vaccines against influenza,[2] there are inadequate market forces or

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

[2] The M&S-WG focused on MCMs to defend against the malicious release of CBRN agents, rather than medical products for 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 making improvements in medical products can often harness existing technologies, the barriers and incentives to the development of influenza MCMs differ greatly from those relevant to MCM development against CBRN agents and are not considered in this report.

other incentives to sustain a vibrant, responsive, and flexible industrial base for developing MCMs against CBRN agents without substantial government investment and path-clearing. A sustained and adequately resourced national effort must address a broad spectrum of CBRN threats. Inconsistent and inadequate funding for MCM development over the past 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 Development Authority (BARDA) within the U.S. Department of Health and Human Services (HHS); the option for an Emergency Use Authorization (EUA);[3] rules of evidence needed to demonstrate the effectiveness of new drugs when human efficacy studies are not ethical or feasible (i.e., the "animal rule"); the recent agreement between the 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 dealt with.[5] The scarcity of MCMs for pediatric use is especially troubling. Another 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 2007 Homeland Security Presidential Directive (HSPD)-18 appropriately cites the need for an "integrated approach to MCM development against CBRN agents 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 and Drug Administration (FDA) (see Table 1). The DoD has been actively researching and developing multiple drugs and vaccines for decades.[6] The 2001 anthrax

[3] Under section 564 of the Federal Food, Drug and Cosmetic Act (21 USC 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

attacks focused attention on the need to accelerate the development of MCMs against CBRN agents to protect civilians, as well as military personnel. Yet the past eight years have seen only limited progress toward HHS and DoD goals. Admittedly, the development pipeline for new drugs, vaccines, and diagnostics is long, convoluted, and costly, sometimes stretching 10 to 20 years or more.[7] But the progression of promising candidate MCMs into the latter stages of development could be accelerated if adequate resource and effort were applied.

Today's list of needed MCMs against CBRN threats is considerably longer than the list of licensed MCMs currently 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 recently replaced. Several unlicensed MCMs are now available in large quantities that could be deployed with an EUA (e.g., anthrax antitoxins, 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 MCMs 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 type (i.e., each annotated cell) is not equally important for national security. Further complicating MCM development is that various MCMs fall along a spectrum of scientific feasibility. For example, the production of safe and effective MCMs 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 MCM development, based on threat assessments and the state of the science for each MCM.

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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.

[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 Medical Countermeasures[9] (MCMs) 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			✦				✦	
Junín 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				

Key:
A – MCM is licensed or approved by FDA for this use
B – Product is licensed or approved for other uses; eligible for use as MCM under an 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 Joint Biological Agent Identification and Diagnostic System
SNS – MCM is stored in the Strategic National Stockpile
VIG – Vaccinia immune globulin
✦ – Designates MCMs that are neither licensed by FDA nor stocked in the SNS, but are national priorities 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. See 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 MCMs. Biopharmaceutical innovation has come largely 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 in December 2007. The NBSB is a Federal Advisory Committee authorized 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 of special interest to HHS regarding current and future chemical, biological, nuclear, and radiological agents, whether naturally occurring, accidental, or deliberate. The NBSB also provides advice on issues related to public health emergency preparedness and response.

The NBSB charged the MCM Research and Development Working Group with reviewing the intertwined portfolio of activities within HHS and DoD, evaluating effective interagency collaborations, identifying gaps and redundancies in federal research portfolios, and making recommendations to enhance innovation, research, and the development of medical countermeasures.[11]

The NBSB charged the Medical Countermeasure 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 MCMs.
- Identify real and perceived barriers-to-entry that have affected industry participation in the development of MCMs.
- 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 MCMs and how to encourage investment by the private sector in the development, manufacturing, and distribution of MCMs.

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

[10] U.S. Public Law 109-417, codified at Title 42 USC sections 219a and 247d-7f; 120 Stat. 2831 (2006). See www.hhs.gov/aspr/omsph/nbsb.
[11] "Report of the NBSB Medical Countermeasure Research and Development Processes for Chemical, Biological, Radiological, and Nuclear (CBRN) Agents," November 18, 2008.

the ways and means needed to develop and sustain fuller engagement by the biotechnology and pharmaceutical industries to support our vital national security mission. …"

NBSB Working Group Inventory of Industry Constraints and Incentives

During its fact-gathering phase with targeted telephone interviews and briefings, 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 the first draft of its "Inventory of Issues Constraining or Enabling Industrial Involvement with Medical Countermeasure Development" and called for public comment in August 2009.[12] Based on this and other feedback, the M&S-WG strengthened and refined the inventory, which is provided in Appendix 1. Next, the M&S-WG drafted a set of recommendations for the U.S. Government to consider as it strengthens the nation's biodefenses.

The inventory is categorized into broad themes of financial, legislative, scientific, human capital, regulatory, and societal issues. Individual entries are placed according to their dominant themes. The inventory 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 MCMs that avoid the resource-intensive nature of a one-bug/one-drug approach. Although broad-spectrum MCMs offer advantages, their probability of successful development is uncertain. Some investment in broad-spectrum MCMs is appropriate, but the current emphasis on targeted MCMs remains prudent, to provide a balanced portfolio.

[12] 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.

Findings of the NBSB Markets and Sustainability Working Group

Assessment of the MCM Enterprise and its Stakeholders

The PHEMCE leads HHS efforts to develop and acquire MCMs that will improve public health emergency preparedness, as well as prevent and mitigate the adverse health consequences associated with CBRN agents and naturally occurring threats. The PHEMCE is an interagency effort led by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) 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 entities; private industry (domestic and international); State, local, and tribal governments; first-responders and healthcare workers; academia;[13] and the public.

DHS issues material threat determinations (MTDs) for those CBRN agents that pose a material threat to national security[14] 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 the type and quantity of specific MCMs 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., pre-exposure prophylaxis, post-exposure prophylaxis, presumptive treatment, definitive treatment), the number of people affected, and the characteristics of the MCMs 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 on the end user's needs).[15]

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

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[13] See, for example, the Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases, www3.niaid.nih.gov/LabsAndResources/resources/rce/

[14] Material threat determinations (MTDs) 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 USC § 247d-6b; see also www.hhs.gov/aspr/barda/requirements.

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

Instead of influenza, if the 2009−2010 scenario had involved the unexpected release of some of the dangerous pathogens identified by DHS as material threats, America would have found itself much more vulnerable, because MCMs 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. Further, the unique needs of children for many MCMs have not been afforded adequate attention or effort.[16]

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

- Routine development of desired MCMs (along the lines of routine pharmaceutical or 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.

Experienced private-sector representatives, who were interviewed for this project, perceive a lengthy process to generate requirements for MCMs. 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 the reliability and sustainability of funding increases industry risk and reduces willingness to participate. Additional questions arise regarding the contract-review process and rate of issuance of new proposals. These issues become even more critical when the full development of an MCM requires the participation of consortia of companies.

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 entities with MCM development activities and regulatory responsibilities remains a concern to industry. In addition to factors identified in the paragraph above, there is also 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 Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and 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., results of disease studies; toxicology reports; access to facilities that possess, use, and transfer select agents and toxins; access to biosafety level-4 facilities), which can require extensive government-industry coordination and prioritization.[17]

[16] See: "National Commission on Children and Disasters, Interim Report." October 2009. www.childrenanddisasters.acf.hhs.gov/.

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

Considering the needs of civilians and military personnel for safe and effective MCMs, the M&S-WG noted that 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 HHS-DoD Integrated Portfolio for developing MCMs against CBRN threats 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.

A confounding concern for industry is that MCM markets are relatively immature. Most of the efforts needed to make markets viable will require making them 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 biotechnology need to be considered from the early stages of development and acquisition. Additionally, the sustainment of MCM markets requires a specific and consistent 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 subprojects involving the remarkable complexity of human biology. And, 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.[18]

The situation for MCM development might be more comparable to that faced by the U.S. Navy or the National Aeronautics and Space Administration (NASA). To build aircraft carriers in the 1930s, the Navy set specifications, and for-profit shipyards built the ships. Additional orders since then have permitted those shipbuilders 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.

[18] HSPD-18, "Medical Countermeasures Against Weapons of Mass Destruction," January 31, 2007. www.fas.org/irp/offdocs/nspd/hspd-18.html.

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., the Other Transaction Authority, OTA) to enable greater collaboration than typically is permitted by the Federal Acquisition Regulations (FAR).[19] But "boom-and-bust" cycles since the 1960s led to the loss of uniquely trained workers, and slowed the pace of space exploration and increased its net expense.

MCM developers also have experienced boom and bust cycles, where starts and stops in congressional appropriations and White House support have led to the layoff 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, based on historic patterns established the 1950s. But the biopharmaceutical industry cannot point to such a precedent for MCMs.

Consider the 10-year Special Reserve Fund of $5.6 billion authorized by the Project BioShield Act in 2004.[20] In FY 2009, $412 million of this reserve was diverted to fund MCMs for pandemic influenza or for advanced research and development.[21] 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).[22] 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[23] must precede procurement, there may be some merit in such a transfer within BARDA's own accounts (if the procurement funds are restored later). But transfers to other entities 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[24] that were developed to bridge the prerogatives and processes of multiple Federal institutions, a modified approach could be

[19] Halchin LE. "Other Transaction (OT) Authority," Congressional Research Service, Report No. RL34760, November 25, 2008.
[20] The Project BioShield Act of 2004 (PL 108-276) is available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ276.108.pdf.
[21] Omnibus Appropriations Act, 2009 (PL 111-8). Gottron F. Project BioShield: Purpose and Authorities, Congressional Research Service, Report No. RS21507, July 6, 2009.
[22] "Budget strips more than $600 million from BioShield program." *Global Security Newswire*, January 8, 2010.
[23] 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 (PL109-417) 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."
[24] For information about the DoD Congressionally Directed Medical Research Programs, see http://cdmrp.army.mil/default.htm.

tested. Because MCM development against CBRN agents 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 U.S. Government (such as a variance 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 could permit their employers to compete for funds under standard Federal Acquisition Regulation (FAR) conditions for requests for proposal (RFPs) that would be released based on their work.

This proposed approach is unusual, but could attract the most-informed advice available. For each Government-established and -prioritized requirement, the MCM integrated product team could review the maturity of the relevant science, the urgency of end-user needs, and appropriate funding levels. The findings of the team (e.g., scientific gaps, industrial shortfalls, potential problems with critical pathways, points of greatest risk of failure) could then be presented to Government leaders to determine which Federal entities would be responsible for each phase of development and acquisition for each MCM. The team could meet on a periodic basis to assess progress toward its goals, based on parameters such as cost, schedule, and performance. This approach assumes that the U.S. Congress continues to fund multiple entities to develop MCMs. An alternative suggestion is to designate one Federal entity responsible for MCM development based on prioritized civilian and DoD-unique requirements and fund that entity adequately. That entity could adopt the process outlined above. Obviously, these proposed approaches need additional detail and discussion.

Approach to Developing MCMs against Radiological and Nuclear Threats

Although most of the efforts of the two NBSB Working Groups were spent considering MCMs against biological threats, the groups also considered the processes in place to develop MCMs against radiological and nuclear threats. The development of both categories of MCMs is highly dependent on animal-model research and specific criteria for assessing safety and efficacy of candidate products. Unfortunately, resources devoted to the development of MCMs against radiological and nuclear threats seem to be less adequate than those applied to biological agents.

To develop MCMs 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 with NIH funding.[25] The prime focus of the MCART consortium is the development of MCMs to treat the major sub-syndromes and organ injury associated with acute radiation syndrome (ARS), and the delayed effects of acute radiation exposure (DEARE). Treatments for these conditions include MCMs 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 MCMs suitable for the SNS. The consortium includes six research sites (three universities, two nonclinical contract research organizations, and one institute); a statistical

[25] See www3.niaid.nih.gov/topics/radnuc.

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 NIH's NIAID Radiation Countermeasures Research and Preparedness Directorate.

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.

HHS and DoD are working together effectively on MCMs for hematopoietic and gastrointestinal radiation exposure syndromes. Another example of DoD and HHS collaboration is the development of MCMs against chemical agents. The Integrated Portfolio for MCM development against CBRN agents exhibits a growing trend throughout the U.S. Government to avoid redundancy.

Evaluation of the Current Situation

The principal barriers hindering industrial involvement in MCM development against CBRN threats 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 entities; (g) inadequate Federal Government understanding of the commercial biopharmaceutical enterprise; and (h) the use of an acquisition system largely intended to procure complex mechanical equipment such as aircraft, vehicles, and ships, rather than support biopharmaceutical product development.

The principal incentives to encourage industrial involvement could include: (a) financial incentives (e.g., grants, tax credits, priority review, 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 MCMs against CBRN agents have not been sufficient to overcome the real and perceived barriers cited in this report. A combination of reducing the barriers and enhancing incentives is needed to harness the full national industrial capacity required to generate and field, as expeditiously as possible, safe and effective MCMs against CBRN threats.

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 MCMs.[26] Additional federal funds likely will be needed for MCM development and acquisition. Inadequate funding delays achieving the goals of MCM licensure, stockpiling, and distribution; 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 funding. Because most MCMs against CBRN agents are in early stages of development, more resources for advanced development will be needed before procurement funds are required. The 10-year Special Reserve Fund for Project BioShield remains a procurement device, not an advanced-development mechanism. But no MCMs will be available to be procured, unless advanced development succeeds first.

   B. Procurement: The Project 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. The U.S. 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

[26] 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 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 Bioterrorism, 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 conclusions." 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).

MCMs are stockpiled and licensed, and an effective distribution process is in place to distribute them quickly or in advance of an event.

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 MCMs against CBRN agents. This leadership, perhaps coordinated at the level of the White House or through a specified Federal entity, is needed to synchronize, prioritize, plan, integrate, and coordinate all essential MCM development activities across Federal entities, 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 eliminate uncertainty about the availability of federal funds. One-year budget cycles for Federal entities (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 MCM 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 MCM development and would reduce industry risk. The U.S. Government could explore the formation of task-specific 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 entities must be willing to innovate and take risks, so they fulfill the public trust to make safe and effective MCMs 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 international partners, State, local, and tribal governments, laboratorians, and first-responders in each of these sectors.** These markets are relatively small, but including them would send industry an important message that the U.S. Government is not the only market. Adding MCMs to Standardized Equipment Lists (SELs) and Authorized Equipment Lists (AELs) would allow State and local first-responders to use federal grant funds to protect these personnel against occupational hazards.

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 MCMs should be assessed for pediatric dosing. For CBRN incidents that arise before an MCM is licensed, that MCM may need to be administered under 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 more mockup pre-EUA dossiers and data sets for the unlicensed/unapproved MCMs 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 in the event of a CBRN attack.

8. **Various departments, agencies, and entities 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 MCMs 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 MCMs 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 MCMs America needs for adequate biodefense.

The enactment of Project BioShield legislation in 2004 provided for a 10-year fund to foster the procurement of medical products that did not yet exist. Although subsequent legislation attempted to target resources for the advanced development of MCMs, MCM funding has never been adequate. Until the Federal Government provides the resources and creates efficient processes for the advanced development of MCMs, 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 MCMs. 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 entities 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 humans 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 entities (e.g., BARDA, CDC, FDA, NIH) 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. These processes echo 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. Overcoming the inherent complexities of human biology for each of multiple MCMs will require substantially more effort than is presently being applied.

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

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

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, and 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 candidate MCM development effort	Decentralized discovery with 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	

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
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) 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)	Current statutory formula: Patent extension supplemented by (1/2 time from IND to filing Biologics License Application (BLA) + full time from BLA filing to FDA approval/licensure) Currently, 5 years of market exclusivity is provided to new chemical entities (NCEs) 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 (PRVs)	Make applicable to biosecurity products	A PRV is a tradable certificate awarded for a licensed treatment for a neglected tropical disease. It entitles the 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? Text of 2007 law at: www.bvgh.org/documents/HR3580-CompromiseFDA-PDUFABill.pdf Draft FDA guidance: www.fda.gov/cber/gdlns/tropicaldisease.htm

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
Limited market size (development costs substantially greater than market potential)	Acquisition Requests for Proposal (RFPs) issued soon after MCM requirements are 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 describe procurement requirements more widely, 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 U.S., as well as State and local governments, civilian first-responders, hospitals, and travel-vaccine providers within the U.S. DoD incorporates this practice to some degree.	Treaty allies represent additional markets, 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 if an attack occurs. DoD has sold MCMs 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 List (AEL), so State and local first-responders can use federal (DHS) grant funds to pay for vaccinations.		Currently only drugs, antidotes, and various treatments are covered, but not vaccines for pre- and post-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. Increase BARDA appropriations for advanced development of CBRN MCMs 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 MCMs. Insufficient funds now allocated.	Multiyear contracting authority (for large molecules, due to complex manufacturing and limited use) and multiyear funding with carry-over authority for R&D and procurement initiatives Manage funding across departments, agencies, and entities as an "integrated portfolio" that mitigates risk by a broad set of target products, with multiple MCMs per disease Base metrics on portfolio performance, rather than individual candidate MCMs 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 1960s. Consistent appropriations for aircraft carriers since late 1930s. Congressional long-term recognition of threats (natural and malicious) and tolerance for candidate 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 MCMs, 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, uncertain development pathways	Cooperative R&D Agreements (CRADAs) allow collaboration with respect for intellectual property. USG 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 USG funding for applied bioscience, material sciences, and biopharmaceutical processes Increase USG 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. USG could lease facilities to private sector. Revenue would support maintenance; industry would not need to invest in their own facilities	Milestone payments could be based 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
	REGULATORY		
Complex, evolving regulatory requirements	Clarify expectations early in product development and minimize revisions during 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 (FD&C Act) and FDA regulations		State and local government requirements for drugs, biologicals, and medical devices that conflict with FD&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 FAR BARDA increases use of OTA for R&D contracts (akin to DARPA) Use CRADAs	Familiarity with FAR (or relief from them)

Problem / Category	Potential Solution	Approach / Advantages / Action	Problem / Limitation / Note
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 senior grades Assure sufficient FDA staff has appropriate security clearances	

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 MCMs within the U.S.	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
	SOCIETAL		
Contribution to national security	Development of MCMs could have spill-over benefits to naturally occurring 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 might 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	Fund and expand coverage of Public Readiness and Emergency Preparedness (PREP) Act to MCMs 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 (FD&C Act) and FDA regulations	Indemnification via 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 Anti-terrorism by Fostering Effective Technologies [SAFETY] Act, within the Homeland Security Act of 2002, 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 health care 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 to develop vaccines that currently do not exist against infectious disease threats in those countries but could 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 a 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 USG has step-in rights if patent arising from federally funded research is not exploited	Bayh-Dole Act of 1980 [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 Commitment
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
CRADA	Cooperative Research and Development Agreement
CRAF	Civil Reserve Air Fleet
DARPA	Defense Advanced Research Projects Agency
DAU	Defense Acquisition University
DEARE	Delayed Effects of Acute Radiation Exposure
DHS	U.S. Department of Homeland Security
DoD	U.S. Department of Defense
DoJ	U.S. Department of Justice
EUA	Emergency Use Authorization
FAR	Federal Acquisition Regulations
FDA	Food and Drug Administration
FD&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 Countermeasure
MTA	Material Threat Assessment
MTD	Material Threat Determination
NASA	National Aeronautics and Space Administration
NBSB	National Biodefense Science Board
NCE	New chemical entity
NHP	Nonhuman 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
PL	Public Law
PREP Act	Public Readiness and Emergency Preparedness Act
PRV	Priority-Review Voucher
R&D	Research and Development
RFP	Request for Proposal
SAFE-T	Support Anti-terrorism by Fostering Effective Technologies
SEL	Standardized Equipment List
SNS	Strategic National Stockpile
TPP	Target Product Profile
UPMC	University of Pittsburgh Medical Center
USC	United States Code
USG	United States Government
VA	U.S. Department of Veterans Affairs
VFC	Vaccines for Children
VIG	Vaccinia Immune Globulin
WG	Working Group
WMD	Weapons of Mass Destruction

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