

**WHERE ARE THE COUNTERMEASURES?
PROTECTING AMERICA'S HEALTH FROM CBRN THREATS**

A REPORT OF THE NATIONAL BIODEFENSE SCIENCE BOARD



March 2010



“We are launching a new initiative that will give us the capacity
to respond faster and more effectively
to bioterrorism or an infectious disease
—a plan that will counter threats at home
and strengthen public health abroad.”

President Barack Obama
State of the Union Address
January 27, 2010

Note: This March 31, 2010 version of this report contains errata on pages 45 and 89. Specifically, language contained in the “Possible Nuclear Scenario” has been changed from “10-kiloton explosion from improvised nuclear device in center of a city, few hundred to 100,000 deaths, number of hospitalizations not estimated” to “Explosion from improvised nuclear device, 10 tons to 10 kilotons, in center of a city, few hundred to 100,000 deaths, number of hospitalizations not estimated.”

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Executive Summary

Robust medical countermeasures are needed to protect America from major national security vulnerabilities.

America faces grave danger from a wide range of chemical, biological, radiological, and nuclear (CBRN) weapons, and from the emergence and spread of infectious diseases. CBRN weapons can cause very large numbers of injuries and deaths, and render affected areas uninhabitable for months or years at a time. Emerging infectious diseases, like the 1918-19 influenza pandemic, have the potential to kill millions. Whether intentional or natural, CBRN agents have the power to incapacitate society and severely damage the economy.

As a matter of national security, America urgently needs to develop medical countermeasures (MCMs) to counter CBRN threats. The federal MCM program to date can be characterized as a good effort conducted by talented people, but lacking in centralized leadership and with poor synchronization of the agencies within the Department of Health and Human Services (HHS). The effort has not fully tapped the talent of the Department of Defense (DoD) and the Department of Homeland Security (DHS). The combined effort is under-resourced and has largely failed to mobilize the productive skills and efforts of industry. There is no unified national strategy that prioritizes the array of threats and encompasses all aspects of responsiveness, from creating to stockpiling to distributing MCMs. Instead, development of MCMs has been too much a matter of selecting projects to fit within available budgets, instead of allocating the necessary funds to tackle a prioritized list of threats. If achieving national MCM goals is likened to climbing a mountain, then most of the mountain remains to be climbed.

In his 2010 State of the Union Address, President Barack Obama called for "a new initiative that will give us the capacity to respond faster and more effectively to bioterrorism or an infectious disease...." The National Biodefense Science Board (NBSB) fully endorses the President's call for a new initiative, and the Board strongly urges that MCMs against chemical, radiological, and nuclear threats be included in the effort.

The need to develop MCMs makes the Secretary of HHS and her agencies responsible for critical elements of national security. On December 1, 2009, HHS Secretary Kathleen Sebelius called for a comprehensive review of the Public Health Emergency Medical Countermeasures

Enterprise (PHEMCE).¹ In response, the Department tasked the NBSB with leading this review, emphasizing an examination of the related strategic management, leadership and accountability structure, and asking for a report synthesizing the issues and challenges facing the PHEMCE.

In its deliberations, the NBSB identified three important themes in the additional effort needed to develop MCMs. The first is *prioritization*: National strategy must proceed from a clear assessment of CBRN threats and subsequent identification of the most urgently needed and attainable MCMs. The second is *synchronization*: Efforts to produce those MCMs must be coordinated across many government agencies and entities, with budgets allocated to ensure smooth transitions from one development stage to the next. The third is *anticipation*: Plans to distribute and dispense MCMs must be devised and realistically tested, so that foreseeable logistical problems are minimized.

Binding these three themes together is the overarching matter of *leadership* of the PHEMCE. Leaders must constantly assess progress and be held accountable for meeting goals. Developing MCMs is a difficult endeavor. Failures and setbacks will inevitably occur. But the leaders must not allow such failures to cause the program to falter. Strong leadership will also be required to keep the many distinct entities from both government and industry working smoothly toward a common set of goals. Agency leaders will need to demonstrate disciplined teamwork to achieve the joint goals. Leadership must also extend into the public sphere, so that the American people understand the need to prepare well and be resilient in the face of CBRN threats.

In its assessment, the NBSB has examined the structure, function, interactions, and written authorities (e.g., law, regulations, charters) of the agencies and Departments relevant to the PHEMCE. Based on all our efforts over the last 30 days, the Board's most important conclusion is that leadership, discipline, and synchronized effort are not lacking, but are unfocused. This problem can be overcome by the HHS Secretary assembling the agency leaders, designating the Assistant Secretary for Preparedness and Response (ASPR) as the coordinating authority, and directing a synchronized, prioritized, common effort toward the Nation's goals.

The NBSB submits the following recommendations for immediate consideration and action.

I. Situational Assessment

Recommendations:²

- 1. The Secretary of HHS, in coordination with Secretaries of Defense and Homeland Security, confers and coordinates with the White House on how best to protect America from CBRN threats, including the merits of establishing a position on the National Security Council (NSC) to lead the relevant National Strategy.**

¹ Remarks of Kathleen Sebelius, HHS Secretary, to the American Medical Association's Third National Congress on Health System Readiness, Washington, DC, December 1, 2009.

² For simplicity, these recommendations typically cite a small number of responsible federal leaders to perform an action. In all such cases, the Board expects and assumes that appropriate coordination within and between Departments and agencies will be conducted.

2. The Secretary of HHS, in coordination with Secretaries of Defense and Homeland Security, coordinates with the White House on a unifying end-to-end National Strategy to address intentional, natural, and emerging CBRN threats.

Now is the time for the U.S. Government to recognize, through expenditure of effort and resources, that MCMs against CBRN threats, of both intentional and natural origins, are a true national security priority. Success against CBRN threats can be defined as the ability to reliably administer all prioritized MCMs to affected individuals within an appropriate period of time to have maximum beneficial effect. The U.S. Government must define clear priorities, focus its efforts and resources on this national security priority, and accelerate the pace and expand the scope of all phases of MCM development—from discovery through administration. The U.S. Government must display the same kind of resolve and persistence that landed humans on the Moon and eliminated multiple infectious diseases from the country.

The U.S. Government agencies involved in MCM discovery, development, acquisition, and fielding³ are doing good and important work. But they are not synchronized, their projects are not prioritized, and oversight from the highest levels of Government is not consistent. These inefficiencies are prolonging America's vulnerabilities. In an orchestra, the identity of the conductor must never be in doubt, or the result is dissonant failure. Similarly, all the players in the development of MCMs must know who is coordinating the whole effort. The development of MCMs for the civilian population is assigned to HHS. The Pandemic and All-Hazards Preparedness Act (PAHPA) clearly assigns the central operational leadership role in addressing end-to-end management for MCM responsiveness to the ASPR. This office must be fully empowered to undertake this role.

Strong support and clear leadership from the White House is also critical. To provide this, the White House should consider restoring a specific functional element to the NSC staff that is focused on creating a unified National Strategy for MCMs, with supportive policies guiding all relevant elements of the US Government for countering the full scope of CBRN threats. Both the threats and the potential countermeasures are many, so they must be operationally prioritized, in a concerted manner.

The Nation needs a single unifying strategy for developing and using CBRN MCMs, so that all understand the Commander-in-Chief's intent for using associated federal assets. Such a strategy, prioritizing the array of intentional and natural threats as well as emerging threats, and encompassing all aspects of responsiveness, does not exist at present.

II. Strategy, Leadership, Priorities, and Accountability

Recommendations:

3. The Secretary of HHS promptly identifies at least three high-priority new MCMs the Department will develop to counter CBRN threats, with target timelines. At least one of these MCMs should address radiation exposure.

³ As used in this report, fielding refers to the efforts to move MCMs from stockpiles to people who need them.

- 4. The Secretary of HHS promptly coordinates with the Secretaries of Defense and Homeland Security to develop prioritized lists of CBRN threats of both natural and intentional origin, to guide further prioritization of MCM efforts.**
- 5. The Secretary of HHS empowers the ASPR as the operational MCM leader, with authority to synchronize the efforts of HHS agencies and with end-to-end oversight.**
- 6. The Secretary of HHS tasks the ASPR to refine the HHS acquisition structure and metrics, to provide accountability for the MCM program.**
- 7. The Secretary of HHS designates the Director of the Biomedical Advanced Research and Development Authority (BARDA) as the MCM Portfolio Director, to coordinate technical aspects of balancing the HHS MCM portfolio.**
- 8. The Secretary of HHS promptly tasks senior HHS leaders to develop a common set of prioritized research goals, prioritized product requirements, and prioritized dispensing goals for civilian populations; and coordinates these priorities with DoD.**
- 9. The Secretary of HHS, in consultation with the Secretary of Homeland Security, develops a plan to overcome existing obstacles that preclude timely distribution and administration of MCMs to people in need (including children and those with limited functional ability).**

A complete prioritization of the many MCM requirements will take some time to create. But the most valuable MCM targets should be apparent after all the work performed to date. HHS should not wait for the full prioritization exercise to be completed. Instead, to crystallize the PHEMCE effort, the Secretary of HHS needs to declare the top three MCMs her Department will develop to counter primary CBRN threats, with target timelines.

During an NBSB workshop, the PHEMCE governance structure was called a structure of consensus, but not a structure of accountability. The NBSB does not see the need for any fundamental reorganization within the agencies involved in PHEMCE, but vigorously recommends that the existing agencies be steered and coordinated with much more common purpose. Common priorities must be adopted and uniformly accepted across agencies, so that national vulnerabilities are resolved as quickly as possible.

The NBSB sees no need for additional management layers; indeed, the Board counsels against additional bureaucracy. Instead, the Board calls for acts of leadership and teamwork by senior officials, and for the ASPR to synchronize the HHS agencies. Also needed is an enhanced team orientation by agency leaders, to work together to achieve the Nation's mutually agreed goals. Figuratively, the HHS agencies are not all pulling on the rope in the same direction – this must change.

Disjointed work leads to waste and delay. With a national strategy in place, HHS in particular must do better in coordinating its multifaceted efforts, adopt shared priorities across HHS agencies, collaborate with government experts outside HHS, and balance its portfolio to defend against multiple threats. Overall accountability has been lacking, and this is a responsibility that the ASPR must assume.

Portfolio prioritization appears to be managed through a top-level approach, but there have been few implementing instructions to HHS agencies on how to achieve the goals. The PHEMCE

would benefit from a central decision authority (i.e., the ASPR) who would properly guide the subsequent development and procurement of MCMs. The BARDA Director should be assigned the duties of Portfolio Director. Then the ASPR needs to report to the Secretary on a periodic basis the Department's progress towards the prioritized goals.

It is in the national interest to have distinct DoD and HHS programs in MCM development, and the Integrated Portfolio approach jointly adopted by these two Departments offers an impressive example of coordination and collaboration that other agencies could well use as a model. Collaboration between DoD and HHS, however, needs to continue to mature and broaden. The Secretary of HHS, in ensuring that agencies within HHS are working toward a common set of priorities, should also make sure that those efforts are coordinated with DoD.

III. Consistent, Adequate, and Balanced Funding

Recommendations:

- 10. The Secretary of HHS promptly determines the coordinated budget requirements for Fiscal Year (FY) 2011 relevant to CBRN MCM budget lines within the National Institutes of Health (NIH), the National Institute of Allergy and Infectious Diseases (NIAID), BARDA, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and ASPR (and in conjunction with DoD), and communicates requests for revision of the President's Budget to the Office of Management and Budget. Secretary gives special attention to FDA resource needs.**
- 11. For FY2012 and beyond, the Secretary of HHS develops a coordinated budget request relevant to CBRN MCM budget lines within NIH, NIAID, BARDA, CDC, FDA, and ASPR (and in conjunction with DoD).**
- 12. The Secretary of HHS develops a legislative plan to seek multi-year funding authority for CBRN MCM efforts.**
- 13. The Secretary of HHS develops a legislative plan to seek appropriate modification and reauthorization of the Project BioShield Special Reserve Fund, before its expiration in 2013.**

A sustained and adequately resourced national effort must address a broad spectrum of CBRN threats. An important conclusion from the NBSB's analysis is that additional federal funds will be needed to provide for the required scope of MCM discovery, development, acquisition, sustainment, and deployment, beyond levels historically provided by the U.S. Government. Inconsistent and inadequate funding for MCM development over the past several decades is simply incompatible with the potential consequences of these threats.

To enhance strategic planning, all HHS agencies involved in MCM development must develop their budget requirements in an integrated manner to achieve the federally prioritized surveillance, research, development, acquisition, sustainment, and fielding goals. The budget requests for NIH, BARDA, CDC, FDA, ASPR, and other relevant agencies need to be submitted to the U.S. Congress as a coherent set of resource needs.

The inherent complexity of MCM development requires time and persistence. The fruits of basic research must transition from discovery into early and advanced development of promising products, with strategic priorities kept in mind at all stages. Such long-term and broad-based planning can be difficult to accomplish in an environment where budgets are decided on an annual basis and distributed over multiple HHS agencies. The Secretary of HHS needs to seek multi-year funding for MCM development, similar to DoD's Program Objective Memorandum (POM) process. Doing so will help demonstrate the U.S. Government's long-term commitment to industry collaborators.

The Project BioShield Special Reserve Fund (SRF) expires in 2013. It needs to be reauthorized and adequately funded. Recently, some of the SRF has been diverted to support other initiatives. This diversion should not happen in the future, regardless of the merit of the other purposes.

IV. Function and Activity

Recommendations:

- 14. The ASPR promptly provides a plan to the Secretary of HHS to provide for centralized advanced development and manufacturing of selected biological MCMs, based on one or more public-private partnerships (PPPs) or federally funded research-and-development centers (FFRDCs).**
- 15. The FDA Commissioner promptly provides a plan to the Secretary of HHS for designating appropriate candidate MCMs for high-priority review, with the appropriate criteria of evidence for safety and efficacy.**
- 16. The FDA Commissioner promptly advises the Secretary of HHS on a plan to revise the draft guidance on the "animal rule."**
- 17. The CDC, BARDA, and NIAID Directors develop a plan for the ASPR for identifying and addressing the need for screening and diagnostic tests for CBRN agents that can be performed in clinical settings, prioritized among other MCM needs.**
- 18. The ASPR, in coordination with leaders of other relevant agencies:**
 - A. Identifies to the Secretary of HHS needs for additional pediatric products for the SNS.**
 - B. Provides to the Secretary of HHS a plan to determine pediatric dosages for at least three MCMs.**
 - C. Identifies to the Secretary of HHS a plan to create and maintain pre-Emergency Use Authorization (EUA) dossiers for the top 20 MCMs, in coordination with DoD.**
 - D. Provides to the Secretary of HHS a plan to write integrated response plans for three high-priority threat scenarios, to describe response from alert to MCM dispensing.**
 - E. Provides to the Secretary of HHS an evaluation of State-level MCM distribution plans to assess adequacy in caring for children and for individuals with functional limitations, and a plan to resolve common problems identified.**

- 19. The NIH Director and NIAID Director provide the Secretary of HHS a plan on how to align NIH resources for MCMs to the national prioritized lists of research goals and product requirements.**
- 20. The Secretary of HHS (working with NIH, NIAID, BARDA, and DoD) develops a plan to rationally allocate limited animal resources and facilities to CBRN animal-model development and testing in alignment with the national prioritized list of research goals.**
- 21. The Secretary of HHS develops a plan to fund the Countermeasures Injury Compensation Program (CICP) for all covered countermeasures, and to extend the filing deadline to a consistent 3-year interval.**

Through collaboration with industry, the U.S. Government has accomplished remarkable public works, including dams, highways, satellites, and weapon systems. A productive relationship between government and industry was forged over the years with aerospace and maritime industries, but has yet to occur with the biotechnology, pharmaceutical, or medical device industries. Effective MCM development requires the U.S. Government to create, sustain, and enhance innovative partnerships with private industry. But the lack of commercial markets for most MCMs, with the exception of influenza countermeasures, means that private industry has little compelling business reason to embark on programs to discover and develop MCMs. Adequate funding and incentives are essential, but no single model can be expected to create sufficient incentives for all MCMs or for all types of industrial partners. Given the need among clinicians for novel antimicrobial agents targeting viruses and bacteria outside a strict definition of biothreat agents, it is clear that the U.S. Government needs to support the development of a new generation of antibiotics and antivirals.

The NBSB concludes that discovery and early development of MCMs is best accomplished through a decentralized system, harnessing the creativity and innovation of the Nation's biotechnology companies. For advanced development and manufacture, more centralized approaches, such as PPPs or FFRDCs offer potential advantages of efficiency and expertise.

At present, MCM developers believe that the standards adopted by the FDA for regulation and review of CBRN MCMs are too often unclear, confusing, and inconsistently applied. The FDA Commissioner needs to lead the development of practical and efficient review criteria for MCMs, and hold FDA staff accountable for MCM activities. This includes devoting significant resources to MCM review. The Commissioner must instill in her staff an understanding of the crucial importance of MCM development to national security and of the vital role the FDA must play. FDA leaders need to find the proper means of according candidate MCMs the review priority they deserve. This may take the form of standards for timely review or priority designation for data packages most important from a national security perspective.

Concern arises particularly from FDA interpretation of the "animal rule," which was devised to address the fact that many MCMs cannot ethically or feasibly be tested in humans. The Board was persuaded by the testimony of many developers and researchers that the FDA's January

2009 draft guidance for industry on the animal rule⁴ contains unrealistic expectations of CBRN MCMs. These include (a) unrealistic expectations for Good Laboratory Practices (GLPs) within high-containment suites, (b) an excessively strict expectation for the pathogen studied in animals to be identical to the etiologic agent that causes human disease, (c) an unreasonably high hurdle for understanding pathophysiologic comparability of the natural history of the disease in humans and animals, and (d) expectations that the potential therapy be studied in other diseases for other conditions of use first.

The FDA Commissioner promptly needs to revise the FDA's draft guidance document on the animal rule (or adopt revisions into a final document), focusing on realistic requirements embodied in the original regulation (e.g., the "reasonably likely" standard of evidence in the rule). Revision should occur within 6 months, after an opportunity for scientific and public-policy input from stakeholders outside the FDA with relevant experience.

A particular weakness in preparedness is lack of information on pediatric dosing for most existing MCMs. Approximately 25% of the American population is younger than 18 years of age, almost 14% is younger than 10 years of age. Many diseases may manifest differently in children and require special diagnostic procedures. HHS should develop an implementation plan and identify resources needed to stockpile appropriate quantities of pediatric doses, ideally pre-packaged and stored in the SNS.

Obtaining EUAs for MCMs that are not yet licensed should not be left until a crisis is at hand. To the extent that some CBRN incidents are anticipatable, the U.S. Government needs to do a better job of assembling additional mockup pre-EUA dossiers and data sets, especially for the unlicensed or unapproved MCMs most likely to be needed or whose availability would be most valuable to society.

Once a particular threat has been identified, challenges remain in assuring readiness to quickly distribute large quantities of appropriate MCMs to local and state emergency managers, and then onward to administration to people in need. More planning and exercises are needed, along with feedback on optimizing delivery and administration in the field, to continue to address identified weaknesses and specific at-risk populations. More integrated response plans need to be written, similar to those already on the shelf for smallpox and pandemic influenza.

A variety of at-risk populations need special attention before, during, and after a CBRN incident. Almost 19% of the American population in 2005 had a disability, including 7% of the population older than 15 years of age who had difficulty with cognitive, mental, or emotional functioning. People living in group quarters or institutionalized settings, as well as children and for adults with functional communication needs (e.g., sensory disabilities, visual disabilities, cognitive disabilities, limited English proficiency) need access to MCMs in customized ways.

Response to a CBRN incident begins with identifying the nature of the threat. Clinical laboratories are not adequately ready to provide accurate diagnosis following exposure and/or

⁴ FDA. Guidance for Industry: Animal Models—Essential Elements to Address Efficacy Under the Animal Rule, January 2009.
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078923.pdf

infection before and during disaster situations. Few tests are FDA-cleared specifically for identification or detection of CBRN threat agents from human samples, and even if such tests are available, relatively few clinical laboratories maintain the trained and experienced personnel and necessary facilities and equipment to provide advanced laboratory testing capability.

V. Enhanced Communication

Recommendations:

- 22. The ASPR provides to the Secretary of HHS a plan to release more information on CBRN consequences to the public, as part of a sustained multi-faceted education and communication plan.**
- 23. The ASPR provides to the Secretary of HHS a plan to make information about MCMs available to the public before and during emergencies in appropriate, accessible and alternative formats.⁵**

Progress in developing and distributing MCMs has been hampered by inadequate communications at many levels. Most fundamentally, the U.S. Government has failed to explain to the American people the urgent need for countermeasures to a variety of CBRN threats. The Federal government needs to prepare threat and risk assessments suitable for public communication, to provide a basis for public engagement on the consequences of CBRN threats. The effectiveness of these communication efforts should be evaluated against standard risk-communication principles.

Better communication with the public, especially from state, local, and tribal health authorities, can lay the groundwork for more effective dispensing and acceptance of MCMs. Such efforts need to take into account the needs of those with disabilities and difficulties with standard information delivery channels.

PHEMCE and ASPR leaders need to think of themselves as leading a very specific type of research and development organization with a distinct primary leader. The primary leader needs to develop a strategy that brands the PHEMCE in such a way that the American public understands the important roles of HHS and ASPR in preparedness and response.

Conclusion

Leaders matter. Leaders prioritize, set goals, and define the mission. When it comes to MCMs against CBRN threats, including emerging infectious diseases, leaders matter. While HHS benefits from many competent leaders, the PHEMCE also needs disciplined followers who can work together as a team toward common, prioritized goals. The vulnerabilities persist until America reaches the goals, together.

⁵ Accessibility means that websites with visual or audio formats, for example, must include versions of those items meaningful to those with vision or hearing impairment. Alternate information formats include Braille, large print, and electronic storage forms such as compact disk or flash drive.

America's enemies will not issue advance warning that they are about to attack with CBRN weapons. Nature will not provide notice that a new infectious disease is about to emerge. MCMs are and must be a national security priority. The path to success in developing an effective MCM program must start with a unifying National Strategy provided by the White House.

Implementation of this Board's recommendations should result in more persistent, innovative, and fruitful efforts to develop the full portfolio of MCMs needed to protect America against CBRN agents. This effort cannot be an uncoordinated series of responses to individual crises. It must be sustained, even in periods of calm, because the road is long and we must have discipline to stay the course. America expects orchestration and unity within HHS's scientific endeavors, not cacophony.

The full report with its recommendations follows.

Common Themes:

Leadership brings it all together.

Prioritize: Focus efforts on the most important, most fruitful work.

Synchronize: Get Departments, agencies, and partners working towards common goals.

Anticipate: Do as much in advance of an incident as possible.

**WHERE ARE THE COUNTERMEASURES?
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Overview and Background

Medical countermeasures are a matter of national security.

The United States of America urgently needs better defenses against weapons based on chemical, biological, radiological, or nuclear (CBRN) agents. This is a serious national security priority, because of the grave peril to American society. CBRN threats can cause very large numbers of injuries and deaths, render affected areas uninhabitable for months at a time, and severely damage the economy.

Natural emerging and re-emerging infectious diseases must also be included within the 'B' of CBRN threat analysis. These include known threats such as pandemic influenza, bacterial pathogens resistant to multiple antibiotics (such as extensively drug-resistant tuberculosis), as well as unexpected outbreaks such as severe acute respiratory syndrome (SARS), which killed hundreds of people in 2002 and caused billions of dollars in economic damage. The influenza pandemic of 1918-20 killed an estimated 50 million people.

The United States must develop, acquire, stockpile, and distribute safe and effective medical countermeasures (MCMs)⁶ – drugs, vaccines, diagnostics, and other products – against CBRN agents that could strike without notice. Despite the ever-present danger, however, both public concern over CBRN threats and U.S. Government action to defend the Nation against them have been inconsistent. Concern and action have tended to rise after events such as the dissemination of *Bacillus anthracis* (anthrax) spores through the U.S. mail in fall 2001 or the emergence of pandemic influenza in 2009, but concern and resolve fade once the danger is perceived to have passed. Public understanding is crucial. If the American public does not demonstrate concern, the U.S. Congress may discount the importance of CBRN preparedness.

⁶ 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).

The federal effort has seen several MCM successes since 2001. When the Secretary of the U.S. Department of Health and Human Services (HHS) committed to drastically expanding the smallpox vaccine supply in 2001, the U.S. Government and the pharmaceutical industry accomplished the task within the next few years. The sponsor of a new cell-culture-grown smallpox vaccine (ACAM2000, Acambis) completed development, clinical trials, and a full regulatory review, and was licensed. That accomplishment, however, involved improving existing technology, not the development of a de novo technology requiring separate proof of concept.

If achieving national goals for developing MCMs is likened to climbing a mountain, then most of the mountain remains to be climbed.

Defending against CBRN threats requires sustained effort and vigilance in the face of a low-probability but high-consequence peril. Achieving national goals will take considerably more effort than has been expended to date. Expending that effort, however, is vital to America's national security. CBRN threat scenarios appear in boxes throughout this document and are summarized at the end of this document.

The Nation's response to the influenza A/H1N1 pandemic of 2009-10 has some limited lessons that can be applied to coping with other outbreaks of novel infectious disease. The limitations arise because the pandemic developed after several years of influenza-specific preparatory effort. Moreover, influenza A/H1N1 can be prevented, treated, or diagnosed with MCMs that are similar to existing vaccines, antiviral drugs, and diagnostics, for which substantial production facilities already exist amid a multi-billion dollar commercial market. To date, the 2009-10 pandemic has involved a virus of relatively low pathogenicity, compared with other influenza pandemics, such as that of 1918. Despite this, there were significant challenges in vaccine development, antiviral distribution and use and deployment of diagnostics. Had the influenza A/H1N1 strain been resistant to stockpiled antiviral drugs, the time required for influenza vaccine production could have resulted in a much greater disease burden. To the extent that accurate, rapid diagnosis was needed to provide guidance for clinical intervention, the Nation was ill-prepared.

In short, the generally successful actions taken by the U.S. Government to deal with the 2009-10 pandemic should not be seen as an indication that the Nation could respond equally effectively to the unexpected release of any of the dangerous pathogens identified as substantial national threats. MCMs against many of these agents and emerging infectious diseases 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.

"We don't know what's coming:
The next public health emergency we face could be much worse."
- Kathleen Sebelius, HHS Secretary, December 1, 2009

In its review, the Congressionally chartered Commission on the Prevention of WMD Proliferation and Terrorism (the "Graham-Talent Commission") gave the U.S. Government a grade of "F" for failing to enhance the Nation's capabilities for rapid response that would prevent biological attacks from inflicting mass casualties. They wrote: "The lack of U.S. capability to rapidly recognize, respond, and recover from a biological attack is the most significant failure identified in this report card."⁷

The need for defense against the human consequences of exposure to CBRN agents has persisted for decades, with too little progress toward a comprehensive cache of MCMs. The federal MCM program to date can be characterized as a good effort conducted by talented people, but currently lacks centralized leadership with authority, is poorly synchronized by agencies within HHS (as well as across Departments), and is under-resourced. This effort has largely failed to mobilize the productive skills of the pharmaceutical, biotechnology, and medical-device industries. Furthermore, there is no single, unifying end-to-end National Strategy from the White House, encompassing all aspects of responsiveness, that prioritizes the array of intentional and natural threats.

To date, the resources provided have not been commensurate with the threat or with the tasks that must be accomplished. Development of MCMs has been too much a matter of selecting projects to fit within available budgets, rather than allocating the necessary budgets to tackle a prioritized list of threats. Additions to the Strategic National Stockpile (SNS) and other stockpiling measures so far have been determined more by matching appropriations to the MCMs already available than by prioritizing needed MCMs and justifying the resources to develop them.

Unlike the successful efforts of federal research and development funding of numerous health programs (e.g., human immunodeficiency virus (HIV), cancer, heart disease), space exploration, and national defense priorities, the MCM effort has failed to meaningfully leverage itself with private-sector capital and expertise. If the U.S. Government (especially within HHS and its agencies) cannot mobilize its expertise and partner with industry, the American people can expect to remain inadequately prepared to reduce the lethal consequences of CBRN threats. Developing MCMs is a difficult endeavor, even with strong leadership and adequate resources. No one should expect fragmented half-measures to succeed.⁸

A New Initiative

In his 2010 State of the Union Address, President Barack Obama called for "a new initiative that will give us the capacity to respond faster and more effectively to bioterrorism or an infectious disease...."

⁷ Commission on the Prevention of WMD Proliferation and Terrorism. Prevention of WMD Proliferation and Terrorism Report Card: An Assessment of the U.S. Government's Progress in Protecting the United States from Weapons of Mass Destruction Proliferation and Terrorism. Washington, DC, January 2010. www.preventwmd.gov/static/docs/report-card.pdf

⁸ A related finding by another panel is acknowledged: 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. www.nap.edu/catalog.php?record_id=10908

The National Biodefense Science Board (NBSB) agrees with the President that a new initiative is needed. The Board adds that countermeasures against chemical, radiological, and nuclear threats must be included in the effort (because so few countermeasures exist for those threats), along with responses to biological agents and emerging infectious diseases. To be effective, a comprehensive MCM program requires unprecedented cooperation and integration across the U.S. Government, private industry, and academia.

Such efforts will have direct benefits in strengthening national security and clinical care. Indirect benefits will accrue by advancing the biomedical sciences generally and enhancing international competitiveness. Further benefits will accrue as this knowledge is applied to combating additional infectious diseases and public health problems.

Prospects for industrial cooperation, however, run up against the stubborn fact that many MCMs against CBRN threats, with the notable exception of influenza countermeasures, have no significant value in typical commercial markets. Development of multiple-use or broad-spectrum products (such as antibiotics useful both as an MCM and for routine infections) could expand such markets, but this approach cannot cover all MCM needs.

Possible Anthrax Scenario:

Anthrax spores dispersed in a line across an urban area – 83,000 to 313,000 people infected, ~ 8,000 to 146,000 develop anthrax disease (varies with speed of antibiotic distribution). Buildings across an area of square miles are abandoned until they can be decontaminated.

Recovery timeline: Months to years.

Sources:

- Baccam P, Boechler M. Public health response to an anthrax attack: An evaluation of vaccination policy options. *Biosecurity & Bioterrorism* 2007;5:26-34.
- Wein LM, Craft DL. Evaluation of public health interventions for anthrax: A report to the Secretary's Council on Public Health Preparedness. *Biosecurity & Bioterrorism* 2005;3:348-56.

True preparedness is not achieved when MCMs have been invented, licensed, and stockpiled in warehouses.⁹ True preparedness requires the ability to dispense MCMs to perhaps millions of individuals in any of more than 3,100 U.S. counties within a few hours, in a way that preserves health, minimizes casualties, and sustains American society. The infrastructure to respond to an event should take advantage of both government and private-sector capabilities in everyday use within our States, counties, cities, and towns whenever possible (a "use-what-we-have" approach). Shifting processes to novel approaches can work, if those new approaches have been exercised ahead of time.

⁹ In FDA regulations, drugs are "approved," vaccines and other biologics are "licensed," and devices may either be "approved" or "cleared." When any of these actions could apply, this document tends to adopt the verb form "license" or "approve" for simplicity.

NBSB: Charge to the Board and Methods

On December 1, 2009, HHS Secretary Kathleen Sebelius called for a comprehensive review of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). The PHEMCE encompasses the effort to define and prioritize MCMs, integrate and coordinate research, product development and procurement activities, and set deployment and use strategies for MCMs within the SNS.¹⁰

As part of the Secretary's review, the HHS Assistant Secretary for Preparedness and Response (ASPR) tasked the NBSB with leading this review, emphasizing an examination of the related strategic management, leadership and accountability structure of the PHEMCE, and asking for a report synthesizing into policy options the issues and challenges facing the PHEMCE.¹¹

The NBSB is a federal advisory committee authorized in December 2006 by the Pandemic and All-Hazards Preparedness Act (PAHPA).¹² The NBSB 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 CBRN agents, whether naturally occurring, or accidentally or deliberately released. The NBSB also provides advice on issues related to public health emergency preparedness and response.

The NBSB charged its Medical Countermeasures Working Group (MCM WG) with examining the strategic management, leadership and accountability structure of the PHEMCE. The MCM WG held a workshop on February 25-26, 2010, in Washington, DC. The workshop included anonymous surveys of participants for observations and suggestions to improve processes. After the workshop, the MCM WG synthesized issues and challenges and developed observations and recommendations, forming the initial drafts of this report. In addition, many members of the MCM WG attended an earlier related workshop conducted by the Institute of Medicine (IOM) on February 22-24, 2010, on strategies to accelerate MCM progress from discovery through licensing.¹³ The MCM WG also considered the work products of previous NBSB WGs.¹⁴

This report, adopted by the NBSB, 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 mass-casualty events and emerging infectious diseases. Pivotal recommendations appear throughout the text and are summarized after the Conclusion. Many other problem-and-solution findings appear in the document (see also Appendix 2).

¹⁰ Remarks of Kathleen Sebelius, HHS Secretary, to the American Medical Association's Third National Congress on Health System Readiness, Washington, DC, December 1, 2009.

¹¹ Letter from ASPR to Chair, NBSB, January 26, 2010

¹² U.S. Public Law 109-417. Title 42 USC sections 219a and 247d-7f; 120 Stat. 2831 (2006). See www.hhs.gov/aspr/omsph/nbsb.

¹³ Institute of Medicine. The Public Health Emergency Medical Countermeasures Enterprise: Innovative Strategies to Enhance Products from Discovery Through Approval. Workshop, February 22-24, 2010. www.iom.edu/Activities/PublicHealth/MedPrep/2010-FEB-22.aspx

¹⁴ National Biodefense Science Board. Optimizing Industrial Involvement in Medical Countermeasure (MCM) Development: A Report of the National Biodefense Science Board (NBSB). Washington, DC: US Department of Health and Human Services, February 2010. www.hhs.gov/aspr/omsph/nbsb/recommendations.html

The PHEMCE is a coordinated interagency effort that builds on federal efforts begun after the attacks of September 11, 2001. The PHEMCE is responsible for:

- defining and prioritizing requirements for public health emergency medical countermeasures;
- coordinating research, early- and late-stage product development, and procurement activities addressing the requirements; and
- establishing deployment and use strategies for medical countermeasures held in the SNS.

The PHEMCE was established in 2006,¹⁵ and is led by the ASPR (see Appendix 3) and includes three HHS agencies (the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH)) and the Biomedical Advanced Research and Development Authority (BARDA). Today, the PHEMCE also includes key interagency partners: the Department of Homeland Security (DHS), the Department of Defense (DoD), the Department of Veterans Affairs (VA), and the Department of Agriculture (USDA). Together, the PHEMCE works to optimize our preparedness for public health emergencies with respect to the creation, stockpiling, and use of medical countermeasures. For a depiction of the relationships of the agencies involved in developing MCMs, see Figure 1.

Within the Office of ASPR is BARDA. BARDA is responsible for advanced research and development of promising new MCMs to meet the government's civilian needs. BARDA is the focal point for industry and academic institutions to obtain necessary guidance, technical assistance, and funding. BARDA casts a wide net in search of promising research on potential MCMs being developed domestically and abroad, and enables HHS to bring products further along the development pipeline. BARDA was established by PAHPA with the expectation that it would make HHS more dynamic, nimble, and accountable.

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;¹⁶ and the public.

¹⁵ HHS Office of Public Health Emergency Preparedness; Statement of Organization, Functions, and Delegations of Authority. *Fed Reg* 2006;71(Jul 6):38403-5. HHS Office of Public Health Emergency Preparedness. Draft HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy for Chemical, Biological, Radiological and Nuclear (CBRN) Threats. *Fed Reg* 2006;71(Sep 8):53097-102.

¹⁶ See, for example, the Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases, www3.niaid.nih.gov/LabsAndResources/resources/rce/

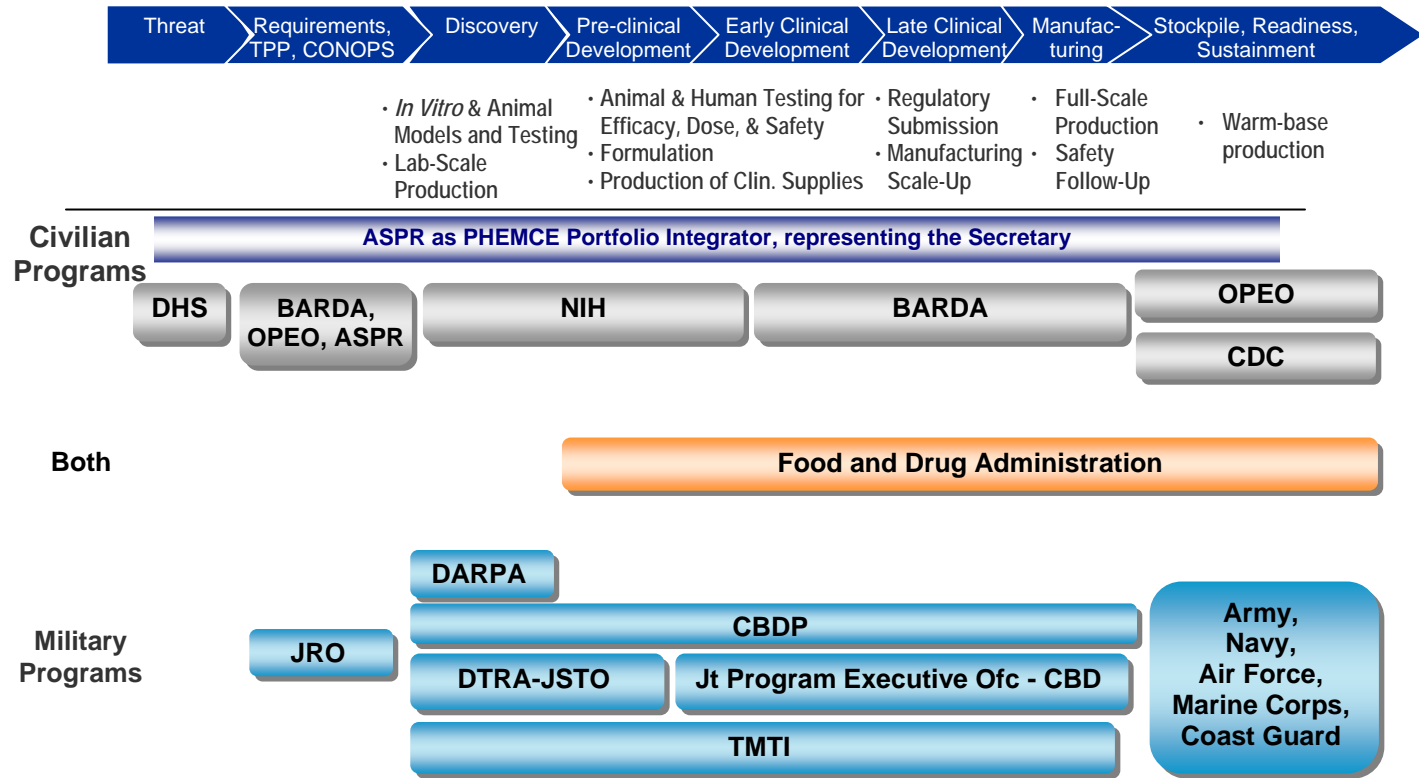
Possible Botulism Scenario:

Botulism toxin introduced into milk-processing facility, ~ 100,000 to 568,000 people poisoned, 28% to 99% of whom are children. Perhaps 60% of poisoned individuals would require mechanical ventilation, far surpassing the number of ventilators available. Death rate in large-scale attack could range from 25% to 60%. Public anxiety over security of milk-distribution system.

Community recovery timeline: Months

Source: Wein LM, Liu Y. Analyzing a bioterror attack on the food supply: The case of botulinum toxin in milk. *Proceedings of the National Academy of Sciences of the USA* 2005;102(Jul 12):9984-9.

Figure 1. Phases of Medical Countermeasure Development and Federal Agencies Responsible for Activities During Those Phases.



- Key:
- ASPR Assistant Secretary for Preparedness and Response
 - BARDA Biomedical Advanced Research Development Authority
 - CDC Centers for Disease Control and Prevention
 - CBDP Chemical and Biological Defense Program
 - CONOPS Concept of Operations
 - DARPA Defense Advanced Research Projects Agency
 - DHS U.S. Department of Homeland Security
 - DOD U.S. Department of Defense
 - JPEO-CBD Joint Program Executive Office for Chemical/Biological Defense
 - JRO Joint Research Office
 - JSTO Joint Science and Technology Office
 - NIAID National Institute for Allergy and Infectious Diseases
 - NIH National Institutes of Health
 - OPEO Office of Preparedness and Emergency Operations
 - PHEMCE Public Health Emergency Medical Countermeasures Enterprise
 - TMTI Transformational Medical Technologies Initiative
 - TPP Target Product Profiles

Sources: U.S. Department of Health and Human Services and U.S. Department of Defense

I. Situational Assessment

Since the 2001 anthrax attacks, the U.S. Government has made several important advances to facilitate MCM research, development, acquisition, and use. These advances include, among others:

- Authorization of \$5.6 billion in funding over 10 years for advanced development and purchase of priority MCMs via the Project BioShield Act of 2004 (PL 108-276);¹⁷
- Creation of BARDA within HHS,¹⁸ with its milestone-payment and other authorities;
- The option for Emergency Use Authorizations (EUAs) for drugs, biologics (including vaccines), and devices (including diagnostics) that have not yet been approved, licensed, or cleared by the FDA;¹⁹
- Rules of evidence to demonstrate the effectiveness of new drugs when human efficacy studies are not ethical or feasible (i.e., the "animal rule");²⁰
- Agreement between HHS and DoD for an "Integrated Portfolio" approach to MCM development;²¹
- PHEMCE stakeholder meetings and workshops,²²
- Adoption of common definitions for Technology Readiness Levels (TRLs) for MCMs by BARDA and DoD;²³

The U.S. Government workers involved in MCM discovery, development, acquisition, and fielding are doing good and important work. But they are not synchronized, their projects are not prioritized, and oversight from the highest levels of Government is neither consistent nor evident. These inefficiencies are prolonging America's vulnerabilities.

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 development. However, despite substantial federal investment, our Nation still possesses neither an integrated National Strategy nor the arsenal of defenses it needs to protect itself from CBRN threats. Further, the unique needs of children for

¹⁷ See www.hhs.gov/aspr/barda/bioshield/index.html

¹⁸ For details, see www.hhs.gov/aspr/barda/

¹⁹ See 21 USC 360bbb-3. For details, see www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

²⁰ 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. 21 CFR 314.600 and 601.90

²¹ Portfolio Advisory Committee (PAC) Charter, the Integrated Portfolio for CBRN Medical Countermeasures (Integrated Portfolio), January 6, 2010. See <https://www.medicalcountermeasures.gov/BARDA/RandD/RandD.aspx>.

²² For details, see www.medicalcountermeasures.gov. HHS Office of Public Health Emergency Medical Countermeasures (OPHEMC): Notice of meeting. *Fed Reg* 2006;71(Aug 21):48547-8.

²³ TRLs provide a common set of definitions to determine the progress and status of research and development programs for MCMs, and allow a candidate product to be classified by degree of maturity. See www.medicalcountermeasures.gov/Integrated_TRLs.aspx.

MCMs have not been afforded adequate attention or effort.²⁴ Accurate pediatric dosing information for many existing MCMs is not known, and pediatric formulations often are non-existent or difficult to obtain in sufficient quantities.

Ultimately, MCMs can do no good if they do not reach the people who need them. Comprehensive and tested plans to distribute and dispense MCMs, developed in close cooperation with State, local, and tribal health authorities, are urgently needed.

"The ultimate goal of this review is a modernized countermeasure production process where we have more promising discoveries, more advanced development, more robust manufacturing, better stockpiling, and more advanced distribution practices."

- Kathleen Sebelius, HHS Secretary, December 1, 2009

Today's list of needed MCMs against CBRN threats is considerably longer than the list of licensed MCMs currently in the SNS.²⁵ Many pathogen targets lack effective countermeasures.²⁶ Moreover, the development pipeline for new drugs, vaccines, screening tools, and diagnostics is long, convoluted, and costly, sometimes stretching 10 to 20 years or more.²⁷

Table 1 summarizes the current status of existing and needed MCMs according to their regulatory and SNS status. It is important to note that the threats (i.e., the rows in Table 1) do not have equivalent clinical consequences, 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 considered a lesser technical and programmatic challenge than the development of filovirus therapeutics or vaccines (e.g., for Ebola and Marburg viruses).

²⁴ National Commission on Children and Disasters, Interim Report. October 2009. www.childrenanddisasters.acf.hhs.gov/

²⁵ 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.

²⁶ 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

²⁷ Matheny J, Mair M, Mulcahy A, Smith BT. Incentives for biodefense countermeasure development. *Biosecure Bioterror* 2007;5(Sep):228-38. Munos B. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews* 2009;9:59-68. Barrett ADT, Beasley DWC. Development pathway for biodefense vaccines. *Vaccine* 2009;27:D2-7.

Table 1. Top-Priority Medical Countermeasures²⁸ Against Chemical, Biological, Radiological, and Nuclear Threats, by License and Stockpile Status

	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			

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 MCMs that are neither licensed by FDA nor stocked by SNS, but are national priorities and being pursued by HHS.

²⁸ 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

DoD has been actively researching and developing multiple drugs, vaccines, and diagnostics for biological and chemical threats for decades.²⁹ DoD's CBRN programs address a list of targeted diseases and toxins that has a moderate degree of overlap with the needs of the American public. By law, DoD must concern itself with potential threats posed to the unique population of deployed troops. The 2001 anthrax attacks focused attention on the need to accelerate the development of MCMs against CBRN agents to protect civilians as well as military personnel.

Measured against the Nation's overall needs, the past eight years have seen only limited progress toward HHS and DoD goals. Some product successes have been achieved. One addition to the SNS is the current smallpox vaccine (ACAM2000), which is produced with a more modern manufacturing process than the vaccine it recently replaced. Several unlicensed MCMs, such as anthrax antitoxins and botulism antitoxin, are now available in large quantities that possibly could be deployed in a declared emergency with an EUA. Large quantities of antibiotics and other supplies also have been stockpiled, but their usefulness for antibiotic-resistant pathogens and suitability for children is limited.

The NBSB's assessment has examined structure, function, interactions, and written authorities (e.g., law, regulations, charters) of the agencies and Departments relevant to the PHEMCE. Based on all our efforts over the last 30 days, the Board's most important conclusion is that leadership, discipline, and synchronized effort are not lacking, but are unfocused. This problem can be overcome by the HHS Secretary assembling the agency leaders, designating the ASPR as the coordinating authority, and directing a synchronized, prioritized, common effort toward the Nation's goals.

Set a Clear Strategy

Ensuring that the PHEMCE embodies national strategies on MCM development is a matter of leadership. Multiple federal documents have been issued that contribute to a national "strategy" for CBRN MCMs,³⁰ but the proliferation of these documents reduces clarity on the Nation's most important MCM goals, rather than facilitating the effort. The Nation needs a single unifying strategy for developing and using CBRN MCMs, so that all understand the Commander-in-Chief's intent for using associated federal assets.

Then, HHS needs to issue an integrated family of strategies and implementation plans that flows from the National Strategy, comprising component strategies and plans for requirement-setting, research, acquisition and development, distribution and dispensing of MCMs, and other response

²⁹ 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.

³⁰ Examples: (a) Homeland Security Presidential Directive (HSPD) 18, *Medical Countermeasures Against Weapons of Mass Destruction*, January 31, 2007 (www.fas.org/irp/offdocs/nspd/hspd-18.html). (b) HSPD-10: *Biodefense for the 21st Century*, April 28, 2004 (www.fas.org/irp/offdocs/nspd/hspd-10.html). (c) HSPD-21: *Public Health and Medical Preparedness*, October 18, 2007 (www.fas.org/irp/offdocs/nspd/hspd-21.htm). (d) *National Health Security Strategy* December 2009, www.hhs.gov/aspr/opsp/nhss/index.html. (e) *National Strategy for Countering Biological Threats*, December 9, 2009, www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf

efforts. While the unifying end-to-end National Strategy is under development, the White House staff should advise HHS which of the national strategy documents should be the primary basis for the PHEMCE.

Now is the time for the U.S. Government to recognize that MCMs against CBRN threats, of both intentional and natural origins, are an explicit national security priority. The U.S. Government must define clear priorities, focus its efforts and resources on this national security priority, and accelerate the pace and expand the scope of end-to-end MCM development (from discovery to administration), displaying the same kind of resolve and persistence it took to land humans on the Moon and eliminate multiple infectious diseases from the country.

Given all this, success against CBRN threats can be defined as the ability, following a CBRN incident or emergence of a disease, to reliably put all prioritized MCMs within the reach of affected individuals in time for those MCMs to have maximum value to protect people. The time interval could range from minutes (e.g., atropine after nerve-agent exposure) to hours (e.g., potassium iodide to protect against thyroid cancer after certain radiation releases) to days (e.g., antibiotics). Meeting this end-to-end goal requires unprecedented integration of effort and resources across the U.S. Government, industry, academia, along with coordination with programs underway in other nations.

Centralized leadership is critical to formalizing this unifying mission and vision. To accomplish this, the White House should consider restoring a specific functional element to the National Security Council (NSC) staff, focused on creating a unifying National Strategy with supportive policies encompassing all appropriate elements of the U.S. Government for countering the full scope of CBRN threats. Both the threats and the potential countermeasures are many, so they must be operationally prioritized, also in a centralized manner, with HHS playing the lead operational role. Without more centralized leadership it is difficult to coordinate strategic development across Departments and agencies that may have their own strategies, resource constraints, and priorities.

National vulnerability to CBRN threats and infectious diseases does not end when a project is funded, nor when MCMs are produced in adequate quantities. Only when MCMs with appropriate delivery configurations are stockpiled and licensed, and an effective distribution process is in place to deliver them quickly and dispense them to people in need, can it be said that the Nation is truly prepared. The progression of promising candidate MCMs into the latter stages of development and stockpiling can be accelerated, if adequate resource and effort are applied.

If the existing range of MCM expertise and capabilities is likened to an orchestra, then it must be clear who is the orchestra's leader. For HHS, the ASPR needs to provide central operational leadership in addressing end-to-end management for MCM responsiveness. This role and responsibility is clearly stated within authorities granted under PAHPA.

Prioritization needs to be based on threat validity and consequences, drawing on the DHS Integrated CBRN Risk Assessment. Each HHS division needs to account for what it is doing to

contribute to success: prioritizing the MCMs that will save the most lives or avert the most harm; speeding the development of those most-needed MCMs; procuring and stockpiling those MCMs; expeditiously transporting those MCMs through multiple distribution nodes, until they reach healthcare workers or emergency responders who will hand them over to individual citizens and families. The appropriate number of hours will differ depending on the response scenario: if the time window for useful intervention after a CBRN event is short, then MCMs may need to be dispersed more widely (less centrally) before an incident than for scenarios in which more time for distribution is available. Success is the timely provision of MCMs to save lives in public-health emergencies.

Recommendations:

- 1. The Secretary of HHS, in coordination with Secretaries of Defense and Homeland Security, confers and coordinates with the White House on how best to protect America from CBRN threats, including the merits of establishing a position on the NSC to lead the relevant National Strategy.**
- 2. The Secretary of HHS, in coordination with Secretaries of Defense and Homeland Security, coordinates with the White House on a unifying end-to-end National Strategy to address intentional, natural, and emerging CBRN threats.**

Actual Chlorine Scenario:

Train derailment discharges up to 70 tons of chlorine – 9 deaths, > 525 injuries, relocation of > 5,000 people for up to 9 days.

Community recovery timeline: Weeks.

Sources:

- Buckley RL, Hunter CH, Addis RP, Parker MJ. Modeling dispersion from toxic gas released after a train collision in Graniteville, SC. *Journal of Air & Waste Management Association* 2007;57(Mar):268-78.
- CDC. Public health consequences from hazardous substances acutely released during rail transit—South Carolina, 2005; Selected States, 1999-2004. *Morbidity & Mortality Weekly Report (MMWR)* 2005;54(Jan 28):64-7.

Consider also:

Possible Chlorine Scenario:

Bomb detonates under a tractor-trailer tanker carrying compressed liquid chlorine. Depending on weather conditions and population density, ~ 100 to 11,000 hospitalizations, ~ 20 to 700 fatalities.

Community recovery timeline: Weeks.

Source: Scheulen JJ, Thanner MH, Hsu EB, Latimer CK, Brown J, Kelen GD. Electronic Mass Casualty Assessment and Planning Scenarios (EMCAPS): Development and application of computer modeling to selected National Planning Scenarios for high-consequence events. *Annals of Emergency Medicine* 2009;53(Feb):226-32.

Consider also:

Lehavi O, Leiba A, Dahan Y, Schwartz D, Benin-Goren O, Schwartz R, Augarten A, Ben-Ari J, Ben-Yehuda Y, Weiss G, Levi Y, Bar-Dayyan Y. Lessons learned from chlorine intoxications in swimming pools: The challenge of pediatric mass toxicological events. *Prehospital Disaster Medicine* 2008;23(Jan-Feb):90-5.

II. Strategy, Leadership, Priorities, and Accountability

The PHEMCE is the interagency effort to define and prioritize requirements, focus research, development, and procurement activities, and establish MCM deployment and use strategies. The PHEMCE has been nominally managed by an Enterprise Governance Board (EGB), which finalized its charter in 2008.³¹ The EGB is chaired by the ASPR and includes voting representatives from CDC, FDA, and NIH. The EGB includes key interagency representatives as non-voting ex officio members: DoD, DHS, VA, the Executive Office of the President and other Federal Agencies and Offices as determined by the Chair, e.g., USDA. DoD is a voting member of the EGB for issues pertaining to the Integrated Portfolio for CBRN MCMs (“Integrated Portfolio”), which is managed by a Portfolio Advisory Committee (PAC). In January 2009, the ASPR moved EGB management from BARDA to the ASPR Office of Policy and Strategic Planning. BARDA chairs the Enterprise Executive Committee (EEC), which coordinates tactical activities from EGB-directed strategic policies.

Governance of PHEMCE

The ASPR asked the NBSB to review the leadership aspects of the PHEMCE. The Board quickly became aware of concerns that the PHEMCE suffers from a lack of coherent leadership and coordination, especially in the overall research, procurement, and fielding of MCMs. The Board believes that the individual agencies of the PHEMCE (i.e., ASPR, NIH, BARDA, CDC, FDA) have generally been working well within their individual sets of responsibility, but that these multiple organizational entities, each with unique missions, do not have an overarching authority to whom they are held responsible. There has been insufficient coordination among the agencies to achieve the Nation's priorities in MCM development. Moreover, there are few defined policies or procedures to support such leadership across the involved organizations or enterprise mission. The issue is larger than simply who is in charge, but also must incorporate how that person exercises authority once appointed.

The PHEMCE EGB offered a vehicle for inter-agency dialogue that accounted for the science issues, but focused on decision making at the policy level where science data was missing. Its weakness was the bureaucratic tension both among HHS agencies and among the relevant Cabinet-level Departments. The tension between the EGB and Office of Management and Budget (OMB) officials was also a difficult challenge, because the tendency to apply the most rigorous and failure-proof standards to an inherently risky product-development environment slowed or blocked completely decisions that were timely and warranted, albeit risky.

During the NBSB WG workshop, the PHEMCE structure (including the EGB) was called a structure of consensus, but not a structure of accountability. The NBSB does not see the need for any fundamental reorganization within the agencies involved in the effort, but the Board vigorously recommends that the existing agencies be steered and coordinated with much more common purpose. Common priorities must be adopted, uniformly accepted and adopted across agencies, so that national vulnerabilities are resolved as quickly as possible. The NBSB sees no need for additional management layers (indeed, the Board

³¹ Public Health Emergency Medical Countermeasures (PHEMC) Enterprise Governance Board Charter, signed February 13, 2008.

counsels against additional bureaucracy). Instead, the Board calls for acts of leadership by the ASPR to synchronize the HHS agencies. Equally important is disciplined teamwork by senior officials of those agencies, to work together to achieve their mutually agreed goals.

It is worth noting that major events confronted by PHEMCE leaders during 2009 included changes in the senior leadership across the Executive Branch with the change in Presidential Administration, new leaders in many HHS agencies, as well as the influenza A/H1N1 pandemic and the earthquake in Haiti. Transitions between administrations of the Executive Branch are predictable. Although any given natural disaster may be unexpected, natural disasters occur routinely. Disruptive events like these present a risk for the PHEMCE senior leadership to lose momentum and focus. It will be important in the future to guard against abrupt disruptions in leadership, focus, and direction caused by events such as those cited.

A system can achieve accountability through its leadership or its processes. First, it must be clear which leader of which division is responsible for a particular strategy and result. In this case, there needs to be a greater emphasis on the fact that the PAHPA has indeed named the ASPR the HHS leader and responsible agent for MCMs, with responsibility for preparedness and response overall. Second, specific processes, such as the Acquisition Process broadly described under the framework of the Federal Acquisition Regulations (FAR), can instill accountability within the system and document major decisions and financial expenditures. For the authorities and responsibilities of the ASPR, see Appendix 3.

Work From a Common Set of Priorities

Disjointed work leads to waste and delay. True integration and coordination at a federal level requires workers in distinct agencies and Departments to acknowledge a common set of prioritized threats (based on the DHS Integrated CBRN Risk Assessment), prioritized research goals, prioritized product requirements, and prioritized dispensing goals.

DHS issues material threat determinations (MTDs) for those CBRN agents that pose a material threat to national security³² 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, BARDA (leading an interagency group) assesses the public health consequences of such scenarios and determines if MCMs are needed and feasible, using several threat-specific Enterprise Working Groups. The appropriate Enterprise Working Group develops requirements for the type and quantity of specific MCMs the Nation needs, under various use conditions, for approval by the PHEMCE EGB. 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., screening, diagnosis, pre-exposure prophylaxis, post-exposure prophylaxis, presumptive treatment, definitive treatment,

³² 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.

other intervention), 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).³³

MCM development priorities need to be based on criteria that include such factors as the number of lives and/or life-years vulnerable to the major CBRN threats, morbidity in plausible scenarios, strain on the healthcare system, and ability to continue societal functions. If threats cannot be adequately quantified in a precise way, due to inherent uncertainties in intelligence analysis, then a semi-quantitative or other basis must be adopted, so that the MCM development effort can be rationally focused. Some development priorities may need to be adjusted according to TRLs of available or candidate MCMs or other indices, so that benefit is maximized over short- and long-term horizons. A complete prioritization of the multiple requirements against multiple criteria will take some time. But the most valuable MCM targets should be apparent after all the work performed to date.

During the MCM WG workshop, several leaders expressed the view that radiation exposure is a dominant threat, and that limited options for MCMs in this arena represent a notable vulnerability.³⁴ It is not clear if these statements are a matter of federal doctrine or not. This points out two key issues: (1) A unified and prioritized threat list is needed, to synchronize the effort of individuals and agencies, and (2) MCMs against radiation exposure warrant special attention by HHS.

HHS should not wait for the full prioritization exercise to be completed. Instead, to crystallize the PHEMCE effort, the Secretary of HHS needs to declare the top three MCMs her Department will develop to counter primary CBRN threats, with target timelines. Given the discussion above, one of these MCMs should address radiation exposure.

Enhance HHS-DoD Collaboration

To increase efficiency and maximize synergy, there is a distinct need for HHS and DoD to coordinate and clearly delineate which MCMs will be developed by each of them. For threats that overlap, the Departments need to come to a clear division of responsibility, with an ultimate intent of synergy as much as possible. Because of differing missions and requirements, it is in the National interest to have a DoD program and an HHS program.

The Integrated Portfolio approach adopted by HHS and DoD offers an impressive example of coordination and collaboration that other agencies could well use as a model.³⁵ Sustained effort and leadership support will be needed to bring this concept to its fullest potential. Centralized leadership will facilitate this. HHS and DoD need to continue to harmonize their definitions and

³³ For more information about the process of “Requirements Setting” for MCM development and acquisition, see www.hhs.gov/aspr/barda/requirements/index.html.

³⁴ NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats, 2005. www3.niaid.nih.gov/about/whoWeAre/pdf/RadNucStrategicPlan.pdf

³⁵ Portfolio Advisory Committee (PAC) Charter, the Integrated Portfolio for CBRN Medical Countermeasures (Integrated Portfolio), January 6, 2010. See <https://www.medicalcountermeasures.gov/BARDA/RandD/RandD.aspx>.

work efforts. They must continue and expand their communications sufficiently to support both their common interests and their unique requirements, coordinating with DHS for material threat determinations and risk assessments.

A minor example is the way the two Departments use the term IPTs in different ways (i.e., DoD integrated product teams for specific product-development activities, HHS integrated program teams for assessing approaches to a threat agent across HHS agencies) that can cause confusion and inefficiency. What DoD calls an IPT is termed a product coordinating team (PCT) by HHS. Beyond issues of nomenclature, including FDA representatives on DoD IPTs has helped speed product development and is thus quite desirable. HHS needs to consider including on appropriate work teams FDA personnel (but not those with product-review responsibilities, to avoid conflicts of interest) who could comment on regulatory aspects of development requirements.

Align the HHS Agencies

The HHS agencies that contribute to the PHEMCE do not share common prioritized objectives. The senior leaders in these agencies and entities need to integrate and synchronize their agencies' efforts more fully. The ASPR needs to personally lead this coordination effort among the division leaders, using chairmanship of the PHEMCE Enterprise Governance Board as a means to achieve integration. But it is not merely the chairing of physical meetings that will achieve alignment of agencies with strong traditions and distinct budget authorizations. Rather, the Secretary of HHS needs to delegate to the ASPR the authority and responsibility (including influence on budget processes) to manage CBRN MCM integration across the HHS agencies, and also require from the ASPR a periodic cross-division progress report, describing any disagreements to be resolved.

Adopt Metrics to Track Accountability

Successful implementation of MCM strategies requires strict accountability in the achievement of numerous steps within them, and accountability requires metrics. The NBSB identified some divisional metrics, but no cross-divisional metrics, to assess progress toward MCM development and fielding goals. BARDA has been using a "cost, schedule and performance" set of metrics for detailed internal monthly reporting on each programs. In addition, the ASPR has had and continues to have Key Performance Indicators that are framed more in terms of annual goals. The HHS-DoD Integrated Portfolio group is developing a useful "pipeline map" to show the number of candidate MCMs that are at various stages of product development.

The ASPR needs to assess and adjust current MCM-related performance metrics and, as appropriate, create new metrics and periodic progress reports from government units, industrial partners, and academic centers. Because product licensure can take years, intermediate-stage metrics will be needed for more short-term monitoring. These metrics can help ease the transition when the incumbent ASPR is followed by his or her successor. Examples would include:

- Prioritized lists of threat agents, research goals, MCM goals, distribution goals, and the like.
- Prioritized list of Requirements.
- Status of funded MCM projects (e.g., at the National Institute of Allergy and Infectious Diseases (NIAID), at BARDA), by product type, mode of intervention, phase of development, population(s) covered, funding type (e.g., R01 grant, Cooperative Research and Development Agreement (CRADA), contract), or other parameters.
- Degree of alignment of expenditures with the prioritized lists.
- Average times required to achieve milestones (e.g., time to Investigational New Drug (IND) filing, time from first patient enrolled to last patient/last visit).
- Program-cost reports and reports of progress across the TRLs, with explanations for variance from cost, schedule, performance, or changes in milestones.³⁶

BARDA's annual reports to the U.S. Congress to fulfill the Project BioShield Act offer good examples of program metrics.

Balance MCM Portfolio Across Multiple Axes

Having inherited a portfolio of candidate MCMs in the early 2000s at various stages of maturity, BARDA and its predecessor offices have done a remarkably good job of moving along those candidates that warranted advancement, given the hand that they were dealt and the modest resources appropriated.

Today, there is a need for ASPR and the leaders of the relevant agencies, acting on the prioritized threat list, to make investments more rationally and balance the portfolio of projects and products. Balancing the portfolio is essential to reconcile the disparate characteristics of the great variety of CBRN threats, allowing a mixture of low- and high-risk projects, across short-, medium-, and long-term perspectives. The goal of balancing the MCM portfolio is to optimize the greatest degree of protection for society over time. Balancing may require compromises to mitigate risk, but it is better to make decisions based on explicit choices than to attempt to do all projects with the same priority. Balancing the portfolio needs to take into account:

- (1) categories of threat (i.e., chemical,³⁷ biological, radiological, nuclear³⁸);
- (2) modes of intervention (e.g., screening, diagnosis, pre-exposure prophylaxis, post-exposure prophylaxis, treatment);
- (3) product types (e.g., diagnostic and screening tools, drugs, antibodies, vaccines, other interventions);
- (4) phases of development, including both early- and advanced-development projects;³⁹

³⁶ See www.hhs.gov/aspr/barda/bioshield/annualreport/index.html

³⁷ See, for example, U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), chemdef.apgea.army.mil/ and Countermeasures Against Chemical Threats (CounterACT), www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm

³⁸ See, for example, Armed Forces Radiobiology Research Institute, www.afri.usuhs.mil/ and NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats, 2005. www3.niaid.nih.gov/about/whoWeAre/pdf/RadNucStrategicPlan.pdf

³⁹ There is need for a common 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-

- (5) products for adults and children and other special populations; and
- (6) single- and multiple-use products (i.e., opportunities to use specific MCMs for multiple uses).

A simple view of the present state of balance would suggest that:

- (a) advanced-development projects are underfunded, relative to basic research (Figure 2);
- (b) radiological, nuclear and chemical MCMs are underfunded, relative to biological MCMs (Figure 2);
- (c) MCMs for children have not been adequately addressed on multiple levels; and
- (d) many threats (including seemingly high-priority threats) have no corresponding licensed MCM, whereas third-generation MCMs are being developed for some threats (Table 2).

These imbalances need to be righted. The Secretary of HHS needs to appoint one HHS leader (perhaps the BARDA Director) as the Portfolio Director, responsible for coordinating these efforts from a technical perspective and making recommendations to ASPR for implementation across the agencies. The Portfolio Director needs to be a career executive with pharmaceutical or related technical expertise, not a political appointee, to stabilize the position and allow technical expertise to be a principal attribute of this individual. Then the ASPR, acting under authority delegated from the Secretary, needs to report the degree of alignment and balance to the Secretary on a periodic basis.

A particularly difficult challenge, which does not exist in routine drug development, is to create MCM solutions in a timely manner for unrecognized or genetically modified pathogens. For example, attack with antibiotic-resistant anthrax organisms would pose a greater challenge than the 2001 incidents. The portion of the portfolio allotted to multiple-use technologies may help overcome such problems.

Increase Attention Paid to Diagnostics

Insufficient attention has been paid to laboratory test, bioassay, and medical device capabilities for clinical diagnostic, screening, and interventional use. CDC and DoD have developed test methods and provided reagents and equipment to public health laboratories and the Laboratory Response Network⁴⁰ (LRN) for important biologic threats. Reagents and procedures for performing many of these tests are distributed as "Investigational Use Only" or "Research Use Only" materials that are not FDA-cleared. Granting EUA status for diagnostic tests developed and validated by manufacturers and individual clinical laboratories during the 2009-10 influenza A/H1N1 pandemic was helpful, but was not done in a timely manner. Validation of these tests was especially burdensome and was largely dependent on sharing of specimens by state public health laboratories.

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."

⁴⁰ Laboratory Response Network, www.bt.cdc.gov/lrn/

Responsibility for ensuring availability of clinical laboratory diagnostics has not been adequately addressed within the PHEMCE. Efficient and reliable delivery and use of MCMs in CBRN responses often requires appropriate diagnostic testing in hospitals and other clinical settings. Not only is there a time lag associated with transferring specimens to state public health laboratories or other reference laboratories, but in many cases patients may not meet the restrictive criteria developed by the public health laboratories to reduce the volume of tests requested. HHS needs to identify the processes and agencies responsible for ensuring that clinical laboratories and other healthcare settings have appropriate capacity for CBRN diagnostic tests to guide medical-practice decisions.

Although this report focuses primarily on laboratory diagnosis, other identification or diagnostic procedures may require consideration. Examples include: biodosimetry for radiation exposure; field identification of nerve agents; noncontact screening via microwave energy emitted by the human body; image-based diagnostics via optical-coherence tomography; and hyperspectral/multispectral imaging.

HHS needs to coordinate an integrated approach to ensure that clinical laboratories, as well as public health laboratories, are adequately prepared and resourced to provide clinical laboratory testing necessary to support use of MCMs and to guide critical healthcare decisions in the face of CBRN threats and other public health emergencies.

Develop a "Brand" for PHEMCE

Maintaining a coherent identity for the PHEMCE, given the numerous agencies it involves, is an important element of leadership strategy that can be achieved by branding. Branding is a business strategy, not a logo or an advertising campaign. ASPR should build for the PHEMCE a master brand that applies consistent messaging, as well as a cohesive, uniform look and feel across all agencies, products and services contributing to the effort. As a key element of the branding initiative, ASPR should devise a visual-identity system that consistently portrays the role of the ASPR in the PHEMCE and in response to incidents. Branding includes procedures on how to use graphic elements, such as logos, fonts and color palettes. These procedures provide guidance and best practices for specific applications, such as public meetings, briefings and print materials.

Enhance Acquisition Strategy

Requirement setting and portfolio prioritization require a means for collaborative but authoritative decision-making. The Board applauds HHS's basic infrastructure of Integrated Product Teams for threat analysis, market research, and requirement generation. But the resulting requirements are too often held at a strategic level, with little evidence of hard decision-making consistent with user-based product specifications. Portfolio prioritization appears to be managed through a top-level approach with insufficient communication and implementing instructions to the separate HHS agencies. The PHEMCE would benefit from a central decision authority, who would guide the subsequent development and procurement of MCMs.

HHS needs to implement a life-cycle acquisition management system tailored to the unique challenges of medical-product development risk and regulatory practices. This system needs to reflect medical-industry best practices. With such a set of practices, people designated as Milestone Decision Authorities (MDAs) can direct project teams, employ the metrics, and accept the risks necessary to both develop and sustain the PHEMCE. MDA is the term for an acquisition role, and can be a full-time or part-time responsibility.

HHS needs to designate a tiered set of MDAs for the PHEMCE, preferably at the HHS Secretariat level (e.g., within ASPR), above the operational and staff divisions. These individuals would have direct decision-making authority, including overseeing transitions of product responsibility between HHS agencies. The Board does not believe that substantial organizational changes are necessary in this area, but the designation of such authorities, along with the implementation of a more tailored acquisition process, would greatly enhance the accountability, visibility, cooperation, and decision making for the enterprise. Although the ASPR would be a suitable senior leader to act as MDA, the numerous other responsibilities of that office may make it impractical to add this extra task. Therefore, some tiering of milestone decision-making based on the dollar value or importance of projects is appropriate, with delegation of authorities to a deputy or internal staff officer who would maintain a sustained and consistent oversight of the efforts.

An MDA has direct decision-making authority over a specific program and a set of projects. Importantly, the MDA approves strategic direction, outlining priorities of actions from technology discovery to specific product development and procurement. The MDA ensures that program managers are executing programs that are balanced and feasible, with risks clearly articulated, by weighing requirement priorities against technology capabilities within financial and sustainment means. During the MDA review, program managers present funding profiles for the portfolio of projects against set priorities. This information provides justification or influence as necessary to the Secretary in budget decisions and allocation. It is this overarching strategic decision-making that guides how projects within the portfolio are executed. It is also one pertinent reason that the MDA must be a senior individual within the HHS Secretariat, because those decisions will affect how the operational and staff divisions will build and execute their programs and capabilities.

The MDA approves the goalposts for each individual project in the PHEMCE organizations. Through pre-set decision points, the authority approves cost, schedule, and performance. Program managers develop metrics to guide the development or procurement actions in the different organizations within the enterprise. These metrics can become unifying exit criteria for organizations at pre-specified transition points (e.g., from NIAID to BARDA, from BARDA to CDC). Through the review process, the MDA's decisions convey these criteria to the organizations to assist them in the collaborative teaming necessary to properly execute programs. The MDA initially approves the acquisition strategy for the development and procurement plans. Through periodic reports from program managers, the MDA monitors for compliance and approves significant modifications where necessary to accommodate changes as circumstances dictate. Ultimately, the MDA, briefed by the program manager, carries the responsibility and accountability to decide if the risk-benefit ratios warrant the continuation of each individual

project. The MDA must assume the risk, based on the evidence provided, to decide whether the technology of the product has the capability of meeting the TPP for a designated user need.

An organization may designate several MDAs. However, they all must report to a single authority, such as a Deputy for Acquisition within the ASPR's Office. High-value or sensitive projects will demand the ASPR's personal involvement, but it would be inappropriate for the ASPR to manage an entire portfolio. Therefore, a delineation of authority is both recommended and feasible, as long as overarching strategy and guidance are made clear to the delineated MDAs. A tiered approach based upon the dollar value or impact of projects has been the norm throughout the federal government and could be easily instituted within this program.

The MDA must have procedures in place to support the decision making and oversight requirements noted above. Otherwise, information and personnel involvement will be unique, run the risk of being incomplete and biased, coordination will suffer, and poor decision making will result. Designation of an MDA alone does not resolve the leadership issue. Selection of appropriately knowledgeable program managers is also of crucial importance. A set of procedures must be implemented that allows for high-quality and consistent portrayal of information that will allow the MDA to make informed decisions that increase the enterprise's chance of success.

Fortunately, federal acquisition policy exists that can be easily modified to provide a framework that empowers program managers and the MDA to make informed and effective decisions. This framework will not only have to be adapted to medical-product development, but must be tailored further because of the unique challenges imposed by the low commercial profit margin and high regulatory oversight that MCMs entail. The domain is a highly risky business area requiring large financial investments and appropriate incentives. The metrics, cooperation, and advisory committees need to reflect this environment.

A federal life-cycle acquisition system provides for several actions that would enhance the overall accountability, inter-agency cooperation, standards, and programming of the MCM development and procurement mission. Several components of the necessary structure exist today. The EGB brings pertinent senior-level organizations together to harmonize actions and collaborate. What is missing is a firm head with executive decision-making ability. Today, the oversight is neither continual nor consistent, and decision-making becomes more like consensus-seeking without authority.

The EGB could act as a requirements-policy advisory group that informs the ultimate decision maker. Another advisory group, an MCM Steering Committee, could function as an acquisition advisory committee, bringing divisional perspectives and information forward, to enable decisions concerning program execution. This could also allow for top-end harmonizing and synchronization of efforts as projects approach transition points.

At the ground level, the Integrated Product Teams and the Project Coordination Teams provide an excellent means to assist in the identification of potential requirements and then the execution of identified projects to meet those requirements.

Recommendations:

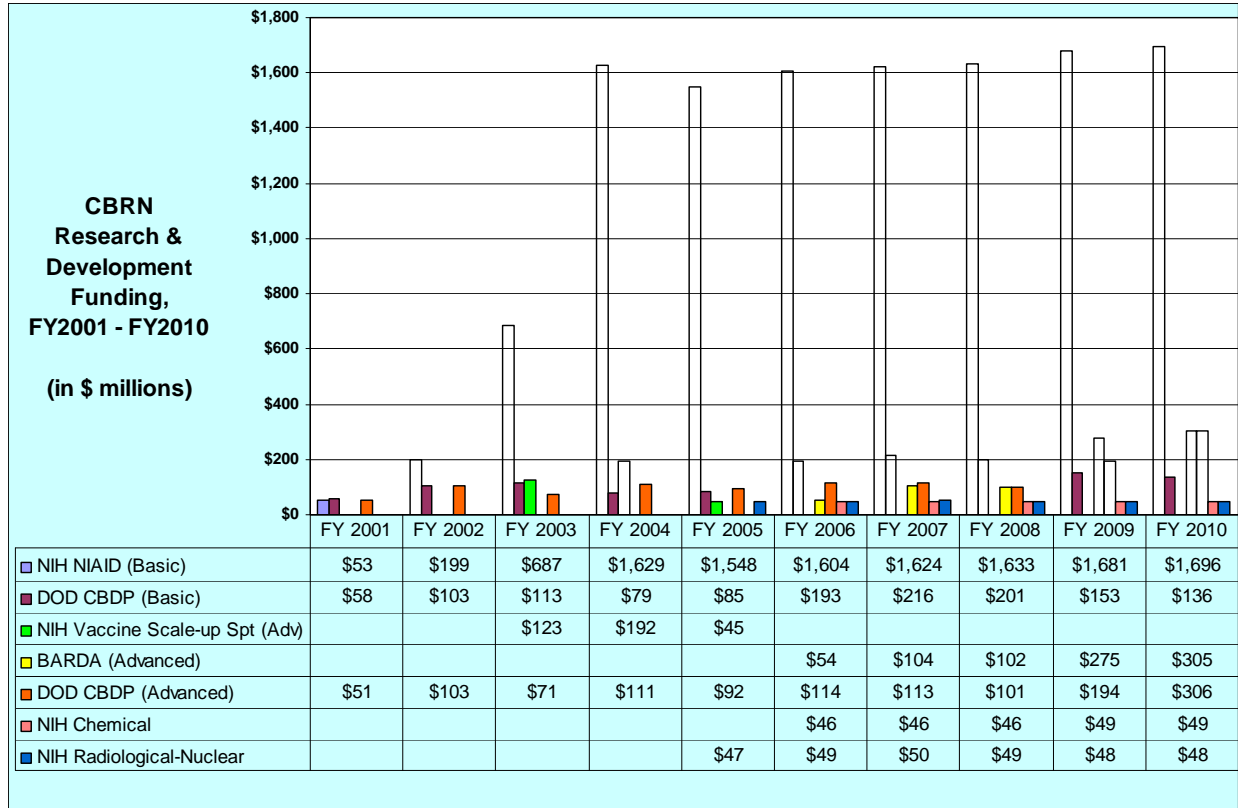
3. The Secretary of HHS promptly identifies at least three high-priority new MCMs the Department will develop to counter CBRN threats, with target timelines. At least one of these MCMs should address radiation exposure.
4. The Secretary of HHS promptly coordinates with the Secretaries of Defense and Homeland Security to develop prioritized lists of CBRN threats of both natural and intentional origin, to guide further prioritization of MCM efforts.
5. The Secretary of HHS empowers the ASPR as the operational MCM leader, with authority to synchronize the efforts of HHS agencies and with end-to-end oversight.
6. The Secretary of HHS tasks the ASPR to refine the HHS acquisition structure and metrics, to provide accountability for the MCM program.
7. The Secretary of HHS designates the Director of the Biomedical Advanced Research and Development Authority (BARDA) as the MCM Portfolio Director, to coordinate technical aspects of balancing the HHS MCM portfolio.
8. The Secretary of HHS promptly tasks senior HHS leaders to develop a common set of prioritized research goals, prioritized product requirements, and prioritized dispensing goals for civilian populations; and coordinates these priorities with DoD.
9. The Secretary of HHS, in consultation with the Secretary of DHS, develops a plan to overcome existing obstacles that preclude timely distribution and administration of MCMs to people in need (including children and those with limited functional ability).

Possible Radiation Scenarios:

- Radiation-dispersal device (RDD) explodes at busy street corner: ~ 30 to 180 deaths.
- Radiation-exposure device (RED) concealed at high-traffic area: ~ 60 to 250 deaths and ~ 130 cases of radiation sickness needing treatment for 30 years. Effect on public behavior. Decontamination efforts for people and objects. Community recovery timeline: Months to years.

Source: Tofani A, Bartolozzi M. Ranking nuclear and radiological terrorism scenarios: The Italian case. *Risk Analysis* 2008;28(Oct):1431-44.

Figure 2. Federal Funds Expended for Medical Countermeasure Research and Development, by Year and Federal Department or Agency



Key:

- BARDA Biomedical Advanced Research Development Authority
- CBDP Chemical and Biological Defense Program
- CBRN Chemical, Biological, Radiological, Nuclear
- DoD Department of Defense
- NIAID National Institute for Allergy and Infectious Disease
- NIH National Institutes of Health

Based on work by Franco, with additional data provided by U.S. Department of Health and Human Services.

Franco C. Billions for Biodefense: Federal Agency Biodefense Funding, FY2009-FY2010. *Biosecurity and Bioterrorism* 2009;7(3):117-33. www.upmc-biosecurity.org/website/resources/publications/2009/2009-09-22-billionsforbiodefense.html

- Prior to 2003, medical countermeasure funding was primarily directed towards U.S. Department of Defense programs.
- FY2003 – FY2006: NIAID funding was focused on early infrastructure development for medical countermeasures.
- FY2007 – Present: NIAID funding focused on medical countermeasure programs.
- NIAID (Basic) category for FY 2009 includes 'basic' research (undirected) (48%), 'applied' research (e.g., target identification, characterization, proof of scientific concept, animal-model development) (38%), 'advanced' research (i.e., preclinical and clinical development) (13%), and construction (1%).
- Figure does include NIH pandemic influenza expenses, as well as construction expenses for biocontainment laboratories. BARDA values exclude pandemic influenza.

III. Consistent, Adequate, and Balanced Funding

The inherent complexity of drug-vaccine-diagnostic development requires time and persistence. The fruits of basic research must transition from discovery into early and advanced development of promising products, with strategic priorities kept in mind at all stages. Such long-term and broad-based planning can be difficult to accomplish in the HHS environment, where budgets are decided on an annual basis and appropriated separately to multiple HHS agencies.

Coordinate Budget Requests

To enhance strategic planning, all HHS agencies involved in MCM development must develop their budget requirements in an integrated manner. The agencies must be able to easily demonstrate that they have stewarded those resources and kept them focused on the federally prioritized surveillance, research, development, acquisition, sustainment, and fielding goals. The budget requests for NIH, BARDA, CDC, FDA, ASPR, and other relevant agencies need to be submitted to the U.S. Congress as a coherent set of resource needs. These budget requirements need to be balanced across early- and advanced-development projects and each of the other categories described in Section II under "*Balance the MCM Portfolio Across Multiple Axes.*" Development of plans for distribution and dispensing of MCMs must also be supported in a manner commensurate with the anticipated production levels of MCMs and the needs of the population.

To best achieve MCM goals, relevant Departments (e.g., HHS, DoD, DHS) should jointly engage the OMB to achieve cross-Department coordination ("cross-cutting") of MCM budget requests.

From a public-accountability perspective, HHS needs to develop a method, without compromising national security, to report its expenditures to the public. Those expenditures should be subdivided by CBRN agent, by MCM, by stage of development (e.g., discovery, early development, advanced development, procurement, stockpiling, such as in Figure 2), and by other relevant parameters of public interest.

Provide Adequate, Sustained Funding

MCM development is expensive, resource-intensive, and time-consuming, with a high level of technical risk. The pathway from requirement to procurement is convoluted.⁴¹ Compounds in the drug-discovery and development process frequently fail for a variety of technical or clinical reasons. As noted in a previous NBSB report,⁴² it is imperative for the U.S. Congress and the Executive Branch (e.g., the OMB) to provide adequate, sustained funding for surveillance, MCM research, development, acquisition, sustainment, distribution, and dispensing capabilities.

⁴¹ See Figure 5, Project BioShield Annual Report to Congress, August 2006—July 2007, www.hhs.gov/aspr/barดา/documents/bioshieldannualreport2006.pdf (page 27).

⁴² Optimizing Industrial Involvement in Medical Countermeasure (MCM) Development: A Report of the National Biodefense Science Board (NBSB). Washington, DC: US Department of Health and Human Services, February 2010. www.hhs.gov/aspr/omsph/nbsb/recommendations.html

Various groups have estimated the range of financial resources needed to support MCM discovery and development. The average cost for full development of each new MCM has been estimated at \$400 million to \$800 million or more over a period of 8 to 12 years.⁴³ To develop several MCM pharmaceuticals over an interval of time, funding requirements ranging from \$1.7 billion to \$3.4 billion per year through 2015 have been proposed.⁴⁴ These estimates include only the cost of developing MCMs. Additional resources would be needed for procurement and initial and sustained inventory.

Failure of individual candidate MCMs during development is fully expected. In other biopharmaceutical research settings, only a small fraction of candidate drugs, vaccines, and diagnostics that enter clinical trials are ultimately licensed by the FDA. There is no reason to expect candidate MCMs to perform any differently. Moreover, MCM development cannot be rapidly accelerated (i.e., “surged”) in any meaningful way in the midst of a crisis, especially for CBRN incidents that could occur without notice.

The Project BioShield Act of 2004 (PL 108-276) was enacted on July 21, 2004, as part of a broad strategy to defend America against the threat of weapons of mass destruction.⁴⁵ The purpose of Project BioShield is to accelerate the research, development, purchase, and availability of effective MCMs. The FY2004 DHS Appropriations Act (PL 108-90) authorized \$5.6 billion in funding over 10 years for advanced development and purchase of priority MCMs via a Special Reserve Fund.

The Project BioShield Special Reserve Fund (SRF) expires in 2013 and needs to be reauthorized and adequately funded. These funds should not be diverted to support other initiatives, regardless of the merit of the other purposes. In FY 2009, \$412 million was diverted from the SRF to fund MCMs for pandemic influenza or for advanced research and development.⁴⁶ 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 NIAID.⁴⁷ Setting aside the merits of other funding targets, repeated diversions of the Special Reserve Fund raise doubts about the intention of the U.S. Government to consistently fund the MCM enterprise over multiple years. Transfers from the SRF to other entities must be avoided if industry confidence in the U.S. Government as a partner is to be fostered.

⁴³ 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, Mulcahy A, Smith BT. Incentives for biodefense countermeasure development. *Biosecur Bioterror* 2007;5(Sep):228-38.

⁴⁴ 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/; 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).

⁴⁵ See www.hhs.gov/aspr/barda/bioshield/index.html. 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

⁴⁶ Omnibus Appropriations Act, 2009 (PL 111-8). Gottron F. Project BioShield: Purpose and Authorities, Congressional Research Service, Report No. RS21507, July 6, 2009.

⁴⁷ “Budget strips more than \$600 million from BioShield program.” *Global Security Newswire*, January 8, 2010.

During the MCM WG workshop, some participants stated that the NIAID allocation for MCM purposes is not inappropriate, but that the appropriations to other Departments and agencies for advanced development, procurement, distribution, and exercises are too small (see Figure 2). The NBSB agrees with this perspective. MCMs clearly must be a national security priority, and appropriate funding needs to follow that principle.

A sustained and adequately resourced national effort must address a broad spectrum of CBRN threats. An important element of the Board's analysis is that the required scope of MCM discovery, development, acquisition, sustainment, and fielding will need additional federal funds, beyond levels historically provided by the U.S. Government. The funds must be dedicated not just to product development, but also to developing the cadre of career professionals at ASPR, CDC, FDA, and other government agencies to enable CBRN preparedness and response functions. Inconsistent and inadequate funding for MCM development over the past several decades is simply incompatible with the potential consequences of these threats. Inadequate funding delays or derails the journey to MCM licensure; the negative impact of inconsistent funding is even more severe, especially for cooperating companies and universities. Additional detail appears in the February 2010 NBSB report.⁴⁸

"Align the funding with the need. NIH funding in CBRN is sufficient. Increase funding for advanced development at BARDA and replenish the Special Reserve Fund."

- Workshop attendee, February 26, 2010

Give Special Attention to FDA Resources

The role of the FDA in determining the safety, efficacy, and quality of drugs, vaccines, and devices (e.g., diagnostics) is as crucial to public acceptance and use of MCMs as it is to everyday medical therapy. Yet the Board concludes that the FDA has not been able to fulfill its implicit national security mission, in large part because of lack of resources.

Evaluating MCMs requires not only sustained urgency on the FDA's part, but in some cases improvements to the regulatory-science base. Many MCMs raise novel regulatory issues, notably an inability to conduct human testing in the usual way, as well as questions about the appropriate risk-benefit criteria for MCMs that would be used only in dire circumstances.

While the FDA has the appropriate structure and ability to tackle these tasks, it is clear from the NBSB's review, the recent IOM workshop, and other advisory panels⁴⁹ that the FDA is

⁴⁸ National Biodefense Science Board. Optimizing Industrial Involvement in Medical Countermeasure (MCM) Development: A Report of the National Biodefense Science Board (NBSB). Washington, DC: US Department of Health and Human Services, February 2010. www.hhs.gov/aspr/omsph/nbsb/recommendations.html

⁴⁹ FDA Science and Mission at Risk. Report of the Subcommittee on Science and Technology, FDA Science Board, November 2007. www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf

drastically under-resourced. It is imperative for America's health and progress for the FDA to be provided adequate resources to bring its regulatory science into the 21st century. Doing so will greatly enhance the FDA's ability to support MCM development and licensing.

The NBSB heard recommendations for other parts of HHS or DoD or other federal entities to transfer some funding from their component budgets to enable unconstrained support for FDA review and other functions. On balance, NBSB prefers to see FDA receive adequate support within its own core appropriation, but acknowledges that pragmatic budget solutions may be needed.

Provide HHS Multi-Year Funding Authority

The year-by-year funding for HHS (unlike DoD), severely constrains planning for MCM development and acquisition, and is a powerful disincentive to industrial partners wishing to enter into long-term cooperative programs with the U.S. Government. HHS needs to be granted this capability, along the lines of DoD's Program Objective Memorandum (POM) process. Synchronization with the DoD POM biennial cycles needs to be considered. Doing so will help demonstrate the U.S. Government's long-term commitment to industry collaborators.

MCM development requires unprecedented cooperation and integration across the U.S. Government and industry, because drug development is a complex, uncertain, long-term process. Multi-year funding with carry-over authority and multi-year contracting authority would signal durable U.S. Government commitment and increase industry's ability to plan coherently or execute MCM development effectively. Multi-year contracting authority is essential to allow long-term planning and eliminate uncertainty about the future availability of federal funds. Programs need to be tied to specific national security goals and subjected to regular progress assessments. Further, HHS agencies should make greater use of reprogramming authority within their appropriated budgets, exercising discretion to move funds among programs in order to speed candidate products through the development pipeline.

Recommendations:

- 10. The Secretary of HHS promptly determines the coordinated budget requirements for Fiscal Year (FY) 2011 relevant to CBRN MCM budget lines within National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), BARDA, Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and ASPR (and in conjunction with DoD), and communicates requests for revision of the President's Budget to the Office of Management and Budget. Secretary gives special attention to FDA resource needs.**
- 11. For FY2012 and beyond, the Secretary of HHS develops a coordinated budget request relevant to CBRN MCM budget lines within NIH, NIAID, BARDA, CDC, FDA, and ASPR (and in conjunction with DoD).**
- 12. The Secretary of HHS develops a legislative plan to seek multi-year funding authority for CBRN MCM efforts.**
- 13. The Secretary of HHS develops a legislative plan to seek appropriate modification and reauthorization of the Project BioShield Special Reserve Fund, before its expiration in 2013.**

Possible Nuclear Scenario:

Explosion from improvised nuclear device, 10 tons to 10 kilotons, in center of a city, few hundred to 100,000 deaths, number of hospitalizations not estimated.

Economic costs: Trillions of dollars.

Community recovery time: Years

Source: Tofani A, Bartolozzi M. Ranking nuclear and radiological terrorism scenarios: The Italian case. *Risk Analysis* 2008;28(Oct):1431-44.

IV. Function and Activity

The federal MCM program to date can be characterized as a good effort conducted by talented people, but one that is poorly synchronized by agencies within HHS.

The balanced-portfolio approach recommended above is intended to assure that the litany of MCM development programs is resourced and managed in concert with the prioritized threats, projects, and goals. In addition, senior leaders within each of the agencies (e.g., NIH, BARDA, CDC, FDA, ASPR) must align and integrate their entity's activities with the prioritized threats, projects, and goals, to expedite development of prioritized MCMs from basic research to licensure, production, and beyond.

Align Efforts to National Priorities

The various Departments and agencies of the U.S. Government must act in concert to ensure success. TPPs for needed MCMs need to be developed with input from end-users (e.g., public-health officials, clinicians, emergency personnel) and then adopted by NIAID and BARDA early and consistently in the development process. Failure to adopt TPPs can waste resources, for example when early development steps must be repeated. Changes to TPPs may be necessary as a candidate product develops and lessons are learned. However, TPP changes should be adopted consciously, because they may delay and increase the cost of product development, if early studies must be repeated with a changed product.

"NIAID biodefense budget/portfolio needs to be aligned and prioritized against defined national security (civilian and military) threats (e.g., against the Material Threat Determinations)."

- Workshop attendee, February 26, 2010

Align Development Pathways with Overarching Strategy

The ultimate purpose of novel countermeasures is to significantly reduce morbidity and mortality in the event of an attack or outbreak. TPPs need to be routinely established early in the process of developing an MCM, consistent with material threat determinations (MTDs) and assessment (MTAs) as well as the concept of operations (CONOPS) to respond to an event. The regulatory path for approval should be calibrated to the nature and potential magnitude of the threat as well as the CONOPS.

During development, the requirements, TPPs, CONOPS, clinical trials, and regulatory pathway (basis for licensing) all need to align. Requirements, TPPS, and CONOPS should undergo periodic re-evaluation. Products with the potential to simplify and increase the effectiveness of CONOPS should receive extra attention, while those found to add marginal or no benefit should either be re-designed or cancelled.

Foster and Accelerate the Research Pipeline

Through collaboration with industry, the U.S. Government has accomplished remarkable public works, including dams, highways, satellites, and weapon systems. A productive relationship between government and industry was forged over the years with aerospace and maritime industries, but has yet to occur with biotechnology, pharmaceuticals, or medical devices. Effective MCM development requires the U.S. Government to create, sustain, and enhance innovative partnerships with private industry to a far greater extent than has recently been common. The lack of commercial markets for most MCMs, with the exception of influenza countermeasures, means that private industry has little compelling business reason to embark on programs to discover and develop MCMs. With adequate resources and effective leadership, however, 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."

Efforts by numerous pharmaceutical and medical-device companies worldwide to tackle, in creative ways, health and disease issues in the developing world show that industry responds to societal concerns, even where markets are limited. In the United States, moreover, private industry repeatedly has shown a willingness to work with the U.S. Government on matters relating to national security. Even granting good intentions, however, harnessing the efforts of private industry requires the U.S. Government to create, sustain, and enhance innovative partnerships. Adequate funding and incentives are essential, but no single incentivizing model will work for all MCMs or for all industrial partners.

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. Discussion of promising technologies at an early, pre-competitive stage can reduce (but not eliminate) some of the risks inherent in MCM development. Some sharing of natural history or biomarker information may help the whole industry, without conferring special advantage on any one company. Private industry may be wary of pre-competitive discussions and collaborations, to avoid possible violations of anti-trust laws. But the HHS Secretary, in conjunction with the Department of Justice and the Federal Trade Commission, has the power to call meetings and codify agreements with industry representatives that under specific conditions are exempt from anti-trust concerns.⁵⁰ The FDA also has certain authorities to call meetings of multiple companies. The biopharmaceutical industry already comes together in standard-setting efforts with the United States Pharmacopeia, training programs coordinated by trade associations, and other venues. These opportunities should be explored more thoroughly.

⁵⁰ Under section 405 of PAHPA. See also Department of Justice. Antitrust Guidelines for Collaborations Among Competitors, April 2000. www.ftc.gov/os/2000/04/ftcdojguidelines.pdf

"So there are gaps at every stage in the process from the laboratory to the factory floor that are slowing or stalling the development of key countermeasures. And in this age of growing public health threats against which countermeasures are often our best defense, that's dangerous."

- Kathleen Sebelius, HHS Secretary, December 1, 2009

Decentralized Discovery with Selected Centralized Development and Manufacture

The U.S. Government needs to continue the current approach of decentralized discovery and adopt centralized advanced development and manufacturing for selected new biological MCM candidates.

- **Discovery and Early Development:** Decentralized discovery harnesses America's scientific creativity and innovation. Much discovery and early development can be expected to come from small, entrepreneurial biotechnology companies that do not have the resident expertise to stay with a candidate MCM into advanced development and production.
- **Advanced Development and Manufacturing:** Technical center(s) of excellence for advanced development and manufacture for selected MCMs increase efficiencies and retention of the knowledge embodied in talented workers experienced in pharmaceutical development and engineering. This approach appears to offer financial and technical advantages, compared to having multiple contract recipients repetitively build development and manufacturing capacity and expertise.⁵¹ Most training in pharmaceutical development is conducted in an apprentice-like manner. Public-private partnerships (PPP, e.g., Sematech) or federally funded research-and-development centers (FFRDCs) offer advantages in developing and retaining the knowledgeable and talented workers needed to develop tomorrow's MCMs. These arrangements need to be developed in a way that respects the intellectual property generated by the discovery team. One or more strategic centralized development and manufacturing facilities could offer a robust suite of pre-clinical, product development, and manufacturing services that could most fruitfully be applied to selected biological MCMs, such as vaccines. Operated by expert personnel employed by industrial partners, the physical plant of this entity might feature a multi-suite flexible manufacturing facility, and perhaps a companion facility for regulatory-science work.

"...we don't just need 21st-century technology. We also need 21st-century financial, legal, and regulatory frameworks that create incentives for companies to build these advanced countermeasures."

- Kathleen Sebelius, HHS Secretary, December 1, 2009

⁵¹ 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>.

Provide Appropriate Incentives

BARDA leaders have described the catalytic role the PHEMCE should play in developing a robust MCM industry. Ideally, this sector of the biopharmaceutical industry would consist of a growing number of successful companies providing MCMs and a substantially larger number of research and development companies focused on unmet MCM needs. Most products already acquired into the SNS (e.g., antibiotics, anthrax vaccine adsorbed, smallpox vaccine) are legacy products for which the technical risks of production were more easily resolved. Table 2 depicts some of the MCM successes and gaps, by mode of intervention.

Development of novel countermeasures for the numerous unmet needs entails considerably greater scientific and technical risk and uncertainty. Various incentives have been proposed to facilitate product development in the private sector. No one incentive will work for all products, nor for all members of a sector of the biopharmaceutical industry. Much discovery and early development can be expected to come from small, entrepreneurial biotechnology companies. These companies may be more likely to respond to incentives in the form of direct payments (e.g., grants, partnerships) or prizes, such as for milestone achievements toward developing MCM candidates.

In contrast to the sparse and poorly capitalized private biodefense industry sector that currently exists, there are extensive privately funded efforts in industry directed at developing novel drugs and vaccines that have generated remarkable progress against HIV, hepatitis B, and hepatitis C. Annual research and development budgets for private entities in this area dwarf the BARDA budget for advanced development. Individuals and insurance plans have shown a willingness to pay tens of thousands of dollars per patient per year for certain therapies; such commercial prices strongly incentivize research to develop these kinds of products. The absence of perceived robust markets, not the sense that the problems are scientifically intractable, is one of the major factors underlying lack of industry or venture-capital funding to develop CBRN MCMs. Commercial market mechanisms are failing to motivate certain kinds of pharmaceutical research, not just in CBRN MCM development, but also in the bacterial-infection arena.⁵²

The strongest incentive to industry may be choices by the U.S. Government to purchase MCMs at prices competitive with commercial products, based on comparable commercialized products in the private market used for analogous purposes. For example, novel CBRN MCM drugs, vaccines, and cell therapies for restoration of bone-marrow function should be priced analogous to other commercial products. FAR § 12.102(f)(1) states that contracting officers “may treat any acquisition of supplies or services that, as determined by the head of the agency, are to be used to facilitate defense against or recovery from nuclear, biological, chemical, or radiological attack, as an acquisition of commercial items.”⁵³ This authority should be used routinely in CBRN MCM acquisitions. This approach to acquisition processes would send a clear and unequivocal signal to the pharmaceutical and biotechnology industries and the capital markets that a robust, sustainable, profitable CBRN countermeasure industrial sector will be created and perpetuated.

⁵² Infectious Diseases Society of America. *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates... A Public Health Crisis Brews*. Arlington, VA, July 2004. <http://www.idsociety.org/badbugsnodrugs.html>

⁵³ Federal Acquisition Regulation Subpart 12.1—Acquisition of Commercial Items—General.

Advanced development and manufacturing is likely to require participation from large, pharmaceutical companies, with experience in product scale-up and process validation, that are accustomed to taking on risky and expensive formulation-development projects. HHS needs to reach out to the senior executives of these companies with explicit requests to support national security goals; these executives may need security clearances to fully understand the situation. These companies are properly concerned about intellectual-property issues, liability issues, and opportunity costs, both from the perspective of their share holders and from their societal responsibilities to continue uninterrupted supplies of routine drugs, vaccines, and diagnostics for day-to-day medical care (e.g., *Haemophilus* vaccines)⁵⁴. These companies may be more likely to respond to direct payments for services rendered and incentives such as tax credits.

Table 2. Selected Biological Pathogens by Mode of Medical Intervention and Developmental Status of Medical Countermeasures

Threat	Pre-Event Prophylaxis	Treatment	Post-Exposure Prophylaxis
Anthrax	Vaccine	Antibiotics + Antitoxin	Antibiotics + Vaccine
Smallpox	Vaccine	None	Vaccine
Plague	None	Antibiotics	Antibiotics
Tularemia	None	Antibiotics	Antibiotics
Viral Hemorrhagic Fevers	None	None	None

Key:

Green cell indicates medical countermeasure (MCM) is licensed or approved by the Food and Drug Administration (FDA) for the microbe specified.

Yellow cell indicates that MCM potentially could be used under an Emergency Use Authorization (EUA) or in an off-label manner.

Red cell indicates that no MCM is available for use under any circumstance within the next few years.

⁵⁴ National Biodefense Science Board. Optimizing Industrial Involvement in Medical Countermeasure (MCM) Development: A Report of the National Biodefense Science Board (NBSB). Washington, DC: US Department of Health and Human Services, February 2010. www.hhs.gov/aspr/omsph/nbsb/recommendations.html

Evaluate Multiple-Use Approaches

Another way to attract private industry's interest may be through "multiple-use" or "platform" technologies. A multiple-use (or dual-use) product is one that fills a desired priority in the U.S. Government's MCM mission, but also has another use or indication with commercial potential, offering a direct incentive to industrial involvement. Broad-spectrum antibiotics and antivirals fall into this category. A platform technology would provide a single backbone that can generate two or more similar drugs, vaccines, or diagnostics, giving it immediate commercial value along with the capability of creating MCMs.

Both approaches have risks and rewards. Broad-spectrum drugs may have serious side-effects, precisely because of the range of cellular targets they are active against. Platform technologies that do not deliver as much as they had promised may nonetheless be difficult to abandon in the face of prospective but unproven future uses. Furthermore, scientific advances that could improve the application for one approach may alter the effectiveness of the active component for the other use, complicating future development of a better drug. From the commercial partner's perspective, adverse information about a CBRN use may affect the reputation of the product for other uses.

The emphasis on "multiple-use" is considered by some portions of the biopharmaceutical industry as a signal that there is and will be no primary market for CBRN MCMs, and that developers should determine how to use the same products for standard commercial uses. No known developer in the hepatitis C or HIV domain is pursuing multiple-use of countermeasures for these enormously challenging agents as a primary strategy.

Multiple-use technology platforms may offer some regulatory advantages, to the extent that approval of the platform for one product may simplify some subsequent approval steps for other products based on the same system. This advantage has yet to be demonstrated in practice, however.

DoD has been pursuing multiple-use products for several years via its Transformational Medical Technologies Initiative (TMTI).⁵⁵ TMTI is intended to spur innovative research to develop broad-spectrum MCMs, as well as technologies to characterize unknown pathogens and rapidly develop medical countermeasures to newly identified threats. The approach is to target common disease pathways or nonspecifically enhance the host's immune system.

Given the need among clinicians for novel antimicrobial agents targeting viruses and bacteria outside a strict definition of biothreat agents, it is clear that the U.S. Government needs to support the development of a new "fleet" of antibiotics and antivirals. In the course of a broad development program, some of those new antimicrobials would be part of the "coast guard," providing substantial value in standard clinical medicine. Others would find utility as part of the "blue-water navy," with value against biological weapons.

On balance, the Board concludes that some investment in multiple-use technologies is appropriate and desirable among a portfolio of many candidate MCMs, but that the multiple-use

⁵⁵ For details, see www.tmti-cbdefense.org.

and platform approaches should not be pursued exclusively. Broad-spectrum pharmaceuticals have been pursued for many decades with limited success. It may be that vaccines are more difficult to develop in a multiple-use or platform technologies than antimicrobial agents or antibodies.

Maximize Markets

As explained in the February 2010 NBSB report,⁵⁶ the U.S. Government needs to expand MCM markets to include international partners, State, local, and tribal governments, certain laboratory workers, 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. Notably, the DoD has led the way in collaborating with counterparts in Canada, Australia, the United Kingdom, and other members of the North Atlantic Treaty Organization (NATO) on MCM development (e.g., plague vaccine, chemical MCMs).

"...we rely on the NIH and Defense Department for most of our early research, but we don't do a great job focusing that research on our top priorities."

- Kathleen Sebelius, HHS Secretary, December 1, 2009

Focus the Basic-Science Agenda

NIH has been entrusted with the lion's share of the CBRN MCM appropriations for the last decade, primarily within NIAID (Figure 2). The Director of NIH, the ASPR, and the Secretary of HHS need to assess the alignment of these resources with the prioritized lists of CBRN threats and products.

NIAID's Office of Biodefense Research Affairs is responsible for management of drug and vaccine development programs, maintenance of a comprehensive preclinical infrastructure to support drug and vaccine efforts, support for animal-model development for use with the FDA's Animal Model Rule, operation of Centers of Excellence in Biodefense and Emerging Infectious Disease, and oversight for extramural construction of biocontainment facilities. The public investment in such resources need to be used strategically to develop CBRN MCMs.

NIAID funds most of these activities through a competitive grant application process. NIAID needs to evaluate whether special NIAID study sections need to be identified to review investigator-initiated grant proposals (e.g., R01, R03) for CBRN topics, due to the unique requirements for studying and developing these products. Or, if necessary, the study sections convened by the NIH Center for Scientific Review should be modified in terms of membership or process to assure recognition of the consequences of CBRN threats in evaluating and prioritizing research proposals. NIAID should use the common prioritized list of MCM needs as eligibility criteria for research proposals (e.g., R01 grants), during the proposal-evaluation

⁵⁶ National Biodefense Science Board. Optimizing Industrial Involvement in Medical Countermeasure (MCM) Development: A Report of the National Biodefense Science Board (NBSB). Washington, DC: US Department of Health and Human Services, February 2010. www.hhs.gov/aspr/omsph/nbsb/recommendations.html

process. In other words, the review and funding of research grants to develop CBRN MCM must be considered under a new paradigm that manifests urgency, reflecting the national security imperative.

NIH should increase its assistance to FDA with development of assays and standards. The recently announced NIH-FDA initiative to advance regulatory science (i.e., the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality) is a step in the right direction.⁵⁷

NIH has the capacity to develop a better understanding of the pathophysiology of various CBRN-related diseases as well as biomarkers and surrogate markers that could be used to assess MCMs on the basis of the FDA's "accelerated approval" regulations,⁵⁸ perhaps without resorting to animal trials. NIH has the capacity and need to develop better evidence on the comparative physiology of non-human primates and humans, so that smaller non-human primate studies could be conducted. In fact, NIH awards contracts to support animal-model development, including models suitable for the "animal rule."⁵⁹ A deliberative process is needed to apportion a finite supply of animals according to the common lists of prioritized research and product needs. These animal resources must be harnessed and shared in a transparent, deliberative process involving the ASPR, so that it aligns with PHEMCE priorities.

At present, several MCM candidates for biological threats await consideration for merit of preclinical and phase I clinical studies (i.e., first use in humans, to assess pharmacologic responses). This situation involves the grant review-cycle time at NIAID and a 2007 informal agreement that BARDA would not manage these types of studies (based in part on budget considerations at the time). The ASPR, using authorities grant in the PAHPA, needs to resolve the status of these products. One possibility is to extend BARDA permission to fund preclinical and phase I studies of promising high-priority MCM candidates at or above TRL 4 (i.e., studies that enable clinical studies in humans). BARDA currently has this prerogative for chemical, radiological, and nuclear MCMs, but not for biological MCMs. Adopting this change would allow for more timely advancement of biological MCM candidates along the development continuum.

Along the product-development path, two major, critical decision gates are encountered:

- Scientific proof of concept (i.e., whether a countermeasure with a specific biological mechanism of action can achieve the predicted, desired biological outcome); and
- Clinical proof of concept (i.e., whether that biological outcome can be achieved in humans within acceptable safety and efficacy parameters).

Scientific proof of concept is central to discovery efforts. Rigorous validation of innovative concepts that could enable novel MCMs is a crucial step in early-phase product development. Clinical proof of concept can be established after the transition from discovery to development.

⁵⁷ See www.nih.gov/news/health/feb2010/od-24.htm

⁵⁸ 21 CFR § 314.500 – 314.560

⁵⁹ *In Vitro* and Animal Models for Infectious Diseases.
www3.niaid.nih.gov/LabsAndResources/resources/dmid/invitro/

Particularly for biologicals, where manufacturing processes effectively define the product (and require additional resources to validate), coordination of the transition between NIH and BARDA will be crucial to ensure an uninterrupted and seamless transition so that evaluation of promising candidates can proceed efficiently. NIH and BARDA need to coordinate portfolio and budget planning with a multi-year perspective, to ensure adequate resources will be available in a timely manner. This process also requires a public component, so that companies within or outside of existing MCM portfolios can access available resources through the NIAID Office of Biodefense Research Affairs and assess availability of downstream funding opportunities that would justify maintaining current development activities.

If BARDA, by analogy to Defense Advanced Research Projects Agency (DARPA), is to fulfill its envisioned and needed role in the rapid development of new concepts (as opposed to deep research to validate concepts in detail), it needs separate funding from the investigator-initiated discovery research enterprise. ASPR requested this authority in budget years 2007-2009 without acceptance by OMB (or HHS budget staff). A similar funding authority is needed for acquisition of products once they are ramped up to full manufacturing capability. This authority would eliminate friction over budget in execution, if not during the formulation phase, and would make clear the choices that senior political leadership is confronting. It is a national security issue.

Address Regulatory Issues

For MCMs to be accepted and used by the American public, it is fully appropriate for MCMs to be reviewed and licensed by the FDA. America wants products that have received FDA's independent assessment of safety, efficacy, and quality. The FDA also plays an important role in the ultimate use of MCMs, insofar as FDA may place restrictions on MCM use. FDA involvement in MCM development, licensing, and fielding presents several challenges that need to be more adequately addressed if MCMs are to be available before they are needed. FDA's Office of Counterterrorism and Emerging Threats (OCET) coordinates a portfolio of FDA policy initiatives, develops FDA strategy, and coordinates EUA activities.

At present, MCM developers believe that interpretation of criteria for regulation and review of CBRN MCMs are too often unclear, confusing, and inconsistently applied across FDA's Centers. Many of these developers express frustration at not knowing what the FDA expects from them. Multiple developers told NBSB members their stories of inconsistent guidance from reviewers, frequent turnover of reviewers, requests for studies of uses other than the use the sponsor intended, and other problems seemingly with roots in inadequate or inconsistent communication. There are several ways to overcome these problems. Common to many of the solutions is the essential need for additional FDA staffing (see Section III), if PHEMCE regulatory and development goals are to be achieved.

It has been difficult for this Board to independently assess developers' cries of frustration, given that FDA rightly keeps confidential its interactions with developers. And the Board has no doubt about the motivation of FDA staff to uphold the interests of public safety. Clearly, they are

dedicated professionals performing crucial tasks with inadequate resources.⁶⁰ Data packages presented to the FDA must present a clear, objective, scientific case for the clinical value of an MCM before any licensing action is deserved. Given the difficulty of developing so many MCMs against such a variety of vastly different diseases, this effort likely represents one of the biggest challenges the FDA has ever confronted. The clear need for expanded FDA staffing and resources was presented in Section III.

Acknowledging that some of data packages in prior MCM submissions may have been inadequate, the Board also believes that FDA needs to consciously reassess "where to set the bar," that is, how much evidence within FDA's scientific discretion is required before an MCM can be approved, licensed, or cleared.⁶¹ This important point is discussed below. In short, FDA should apply reasonable criteria, not futilely attempt to achieve certainty with unanswerable questions.

REGULATORY: THE "ANIMAL RULE"

FDA developed the "animal rule" to address the fact that many MCMs cannot ethically or feasibly be tested in humans in the usual way.⁶² The rule provides for safety and effectiveness testing of MCMs in animal models, with substantial evidence that the animal data is relevant to human efficacy, so that dosing can be calculated accordingly. Safety studies in humans are still required. The animal rule was intended to be enabling, but it has not yet borne much fruit. Only two products since 2002 have gained new medical uses through these regulations: pyridostigmine bromide as a nerve-agent pretreatment and hydroxocobalamin for cyanide poisoning. Each of those products had been approved clinically for other uses for many years. Thus far, no novel MCMs have been developed to licensure or approval through the animal rule regulation.

Moreover, the FDA's January 2009 draft guidance for industry on the animal rule has caused difficulty and confusion.⁶³ Concern over this issue is a major obstacle to full engagement of private industry in MCM development and the efficient conduct of research. As variously interpreted by some FDA review staff, the current animal rule criteria suggest unrealistic understandings of CBRN MCMs. These include (a) unrealistic expectations for GLPs within high-containment suites, (b) an excessively strict expectation for the pathogen studied in animals to be identical to the etiologic agent that causes human disease, (c) an unreasonably high hurdle for understanding pathophysiologic comparability of the natural history of the disease in humans

⁶⁰ FDA Science and Mission at Risk. Report of the Subcommittee on Science and Technology, FDA Science Board, November 2007. www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf

⁶¹ In FDA regulations, drugs are "approved," vaccines and other biologics are "licensed," and devices may either be "approved" or "cleared." When any of these actions could apply, this document tends to adopt the verb form "license" or "approve" for simplicity.

⁶² 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.

⁶³ FDA. Guidance for Industry: Animal Models—Essential Elements to Address Efficacy Under the Animal Rule, January 2009. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078923.pdf

and animals, and (d) expectations that the potential therapy first be studied in other diseases for other conditions of use.

MCM candidates certainly need to be assessed by reliable laboratory methods, under relevant experimental conditions. But setting the bar at unreasonably high levels leaves Americans vulnerable to lethal CBRN agents.

Because of these problems, the FDA Commissioner promptly needs to revise the FDA's draft guidance document on the animal rule (or adopt revisions into a final document), focusing on realistic requirements embodied in the original regulation (e.g., the "reasonably likely" standard of evidence in the rule). Revision should occur within 6 months, after an opportunity for scientific and public-policy input (e.g., a technical workshop, an IOM workshop⁶⁴) from stakeholders outside the FDA with relevant experience. Members of FDA review divisions need to be included in these workshops. FDA also will need to harmonize interpretation of the animal rule across its product-review centers (i.e., the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER)).

REGULATORY: FDA STAFF EDUCATION

All FDA staff members need to understand the potential threats the Nation faces and what public-health emergencies would look like if various threats became real. FDA leaders need to explain CBRN threats and consequences to the staff, assisted by briefings from DHS and national security agencies. For example, ASPR and DoD should describe CBRN scenarios, including potential numbers of fatalities and casualties over a likely time course, so FDA staff can better understand the risk arising from the absence of appropriate MCMs. This understanding will inform the risk-benefit evaluation of an MCM. These briefings should explore circumstances under which administration of an MCM before a catastrophic event may be possible, the limitations of community emergency responses, and what information is likely to be known about people who have been exposed to a threat agent. These issues need to be addressed in a consistent manner across all candidate MCMs.

Briefers should describe likely clinical scenarios, including how many people would have access to antibiotics or other products and over what time course, whether hospitals would have capacity to admit all exposed patients, likely availability of respirators and other sophisticated equipment in a mass-casualty incident, and the extent to which supportive care may be available. This information is needed to properly design animal and clinical studies. Supportive care alone may be an effective mitigator in a CBRN incident. Use of an MCM must be viewed in the context of the scenario and its likely mode of use.

The need for information on CBRN threats, consequences, and treatment scenarios extends to FDA advisory committees. If public members of these committees do not merit security clearances, then FDA should consider limiting the committee's role to assessing product safety and efficacy in the context specified by the PHEMCE procurement contract or the data required to demonstrate efficacy under the animal rule. Issues of need and product specification are

⁶⁴ National Academies of Science. Animal Models for Assessing Countermeasures to Bioterrorism Agents www8.nationalacademies.org/cp/projectview.aspx?key=49112

defined before contract award and are largely moot during final stages of licensing review. Advisory committees should not second-guess these matters and the FDA should charge their advisory committees accordingly.

Another concern arose at the October 27, 2009, meeting of FDA's Anti-Infective Drugs Advisory Committee during evaluation of raxibacumab, a monoclonal anthrax antitoxin. The FDA asked members of the Committee whether additional evidence of efficacy beyond currently approved antibiotics should be requested.⁶⁵ This request contrasts with FDA's own "animal rule," in which FDA stated that its staff "have decided to eliminate the requirement that 'products would be expected to provide meaningful therapeutic benefits to patients over existing treatments,' as well as the limitation that the toxic agent be 'without a proven treatment.'"⁶⁶

A potential source of inconsistency is the application of distinct review processes for similar products by CBER and CDER. For example, polyclonal antibodies (including anthrax antibodies from human plasma) are regulated as blood products by CBER, while monoclonal antibodies (including monoclonal anthrax antibodies) are regulated as therapeutic proteins by CDER. In the absence of harmonization efforts, the development criteria for novel anthrax antibodies could therefore differ between the two Centers. It is important for FDA reviewers to apply consistent criteria for the common aspects of a dichotomy such as this example (e.g., endpoint measurements for safety and efficacy).

REGULATORY: RISK-BENEFIT ASSESSMENTS

In the case of MCMs to counter CBRN agents associated with exceptional morbidity and lethality, FDA can apply several regulatory pathways (e.g., "accelerated approval," the "animal rule"). When FDA has confronted serious health crises in the past, it has adapted its approval criteria to meet the Nations' public health needs. The Board is concerned that FDA review teams may be seeking to resolve uncertainty to such an excessive degree that it becomes difficult for an MCM to earn licensure.

The risk-benefit calculation for all medical-product approvals is customized to their intended uses. A comparison to consider is the health consequences of having no MCMs at all. MCMs may have substantial value against lethal agents, even though the MCMs will inevitably pose some real or hypothetical risks of their own (as do all other drugs). The Secretary needs to make it clear to the FDA Commissioner that, recognizing inevitable uncertainty about safety and efficacy, FDA can and should decide to make MCMs available on the basis of reasonable (but not overwhelming) data and information.

The FDA Commissioner needs to lead the development of practical and efficient regulatory criteria for MCMs. The Commissioner should take an active role in helping staff members recognize that MCM development is an important aspect of national security and that FDA has a

⁶⁵ Final Questions for the October 27, 2009 Meeting of the Anti-Infective Drugs Advisory Committee. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM188445.pdf

⁶⁶ 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. 21 CFR 314.600 and 601.90

vital role to play. The Board heard from developers who consider review times unreasonably slow and from FDA staffers who contend that MCMs receive appropriate priority. This discordance can be addressed by measuring review-cycle times, numbers and timeliness of meetings and comparing these times to non-MCM products accorded accelerated review. Mentoring by senior FDA officials for less experienced review staff members should be useful.

Historically, FDA reviewers have acted with less than perfect data when they approved the first antiviral drugs to treat HIV infection and on multiple other occasions when approving the first agents in a therapeutic class. FDA reviewers make decisions with less than perfect data on a regular basis. FDA already is committed to making MCM decisions on the basis of evidence sufficient for experts to make reasonable judgments regarding safety and efficacy.⁶⁷ FDA should not delay approval of a MCM to obtain data for sub-populations such as the elderly or pediatric uses, but rather should approve the initial data package and require continued studies. Current law and regulations give the FDA specific authority to approve a product with limited data and restrict a product's use to specific circumstances.⁶⁸ FDA needs to take advantage of this option for MCMs whenever appropriate.

The ultimate standard for any FDA licensing action is whether the benefits of the medical product outweigh the risks of that product, taking into account the purpose and circumstances of use. When a disease is severe and other therapies are not available, the risk-benefit equation can shift towards approval of therapies on the basis of less data and in the face of risks that may be greater, although still outweighed by the expected benefits. There are numerous examples of how the FDA has applied a scientifically thoughtful, yet flexible, risk-benefit equation in times of medical need, whether for diseases with high morbidity and mortality or for rare diseases for which studies are very difficult (e.g., HIV antivirals, thalidomide to treat multiple myeloma, drugs to treat multi-drug resistant tuberculosis).

The appropriate standard for licensing of MCMs – how much benefit can be expected and how great a risk is appropriate – is in part a question for society as a whole to consider. FDA is subject to frequent second-guessing by some members of the medical and scientific community, the news media, the public, and the U.S. Congress. FDA should not be expected to determine and then apply a standard without the benefit of guidance from the broader medical and scientific community. FDA needs to publicly develop principles for MCM consideration and then be willing to make MCM decisions expeditiously, while anticipating inevitable criticism.

The FDA Commissioner and Center Directors need to reach out to the medical and scientific community to discuss broadly the appropriate risk-benefit ratio for MCMs. NIH and DoD scientists need to be involved in this discussion and support the FDA. The Secretary of HHS

⁶⁷ 21 CFR 312.84: “FDA’s application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.”

⁶⁸ For example, the FDA Amendments Act of 2007. Subpart E--Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm

must encourage this support from the NIH, to engage the greater scientific community in dialogue about sound medicine and science in the face of residual uncertainty. FDA can in some cases use its advisory committees as part of this process, a step that will permit members of the public to comment on approval criteria. FDA retains the responsibility to determine whether data submitted to it in support of a medical product demonstrate that the criteria have been met.

In cases where animal models are reasonably pertinent, evidence that disease can be mitigated by treatment of animals is highly valuable. Because there are many MCMs to be tested and limited non-human primates (NHP) to test them in, the FDA needs to be judicious in requirements for NHP studies and not attempt to repeat in animals the large trials that are conducted for other disease conditions in humans. The NIH animal-models program needs to work with FDA to prioritize MCM studies to optimize limited animal resources.

FDA can judge the quality of the data presented to it, but it does not have the capacity it needs to conduct scientific studies or to consider new ways of assessing scientific evidence. The Board is encouraged by recent efforts to address regulatory-science issues at the FDA and endorses expansion of such efforts. NIH has the capacity to develop a better understanding of the pathophysiology of various CBRN-related diseases, and the capacity to develop biomarkers and surrogate markers that could be used to assess MCMs on the basis of the FDA's "accelerated approval" regulations,⁶⁹ perhaps without resorting to animal trials. Both NIH and DoD have the capacity and need to develop better evidence on the comparative physiology of non-human primates and humans, so that smaller non-human primate studies could be conducted.

FDA recently announced an expansion of its "Transparency Initiative" to make it more transparent towards industry.⁷⁰ FDA should use its regulatory and guidance processes to make requirements for MCM licensing more transparent. In addition, FDA review divisions need to be encouraged to give binding advice, such as through use of Special Protocol Assessments.⁷¹ FDA needs to assess the reasons why few MCMs have been licensed, and hold workshops to teach MCM developers how to overcome those problems.

REGULATORY: REVIEW PRIORITY

FDA leaders need to accord candidate MCMs the appropriate level of priority within the review process, according to their potential value in an emergency. This may take the form of metrics for timely review or priority designation for data packages most important from a national security perspective. The high degree of morbidity and lethality of CBRN agents must be taken into account throughout this process. If security clearance is necessary for FDA reviewers to understand the threat consequences, then the reviewers need to obtain security clearances.

If the Secretary asks FDA to operate on the premise that an attack could occur at any time, the FDA will want to define the best study options within specified time frames, and support studies that will directly address the value of those products. Because there will always be data gaps for

⁶⁹ 21 CFR § 314.500 – 314.560

⁷⁰ www.fda.gov/AboutFDA/WhatWeDo/FDATransparencyTaskForce/default.htm

⁷¹ Guidance for Industry: Special Protocol Assessment, May 2002.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080571.pdf

MCMs, the FDA should put more emphasis on post-approval data gathering and less emphasis on an exhaustive collection of pre-approval studies.

At its workshop, the MCM WG discussed whether FDA approval, licensure, or clearance is the appropriate standard for utility of MCMs. After exploring the issue from multiple vantage points, most attendees agreed that the appropriate standard is full approval, licensure, or clearance, recognizing that the applicable levels of evidence need to take into account the degree of morbidity or lethality related to the threat agent. A frequently cited reason was that Americans expect to have MCMs available that have been thoroughly evaluated by the FDA.

The NBSB considered whether a separate review division within FDA (perhaps a Center for Emergency Preparedness and Response) is needed to review MCMs more expeditiously. This approach would have the advantage of focusing a set of reviewers on a set of CBRN scenarios and the "animal rule." But it could have the disadvantage of diverting talent from the various technical Centers (e.g., vaccine reviewers could be displaced from CBER and dilute its talent pool). On balance, the NBSB favored FDA leaders finding the proper means of according candidate MCMs the appropriate degree of priority within adequately staffed review divisions. This might take the form of criteria for timely review or priority designation for data packages most important from a national security perspective. If the FDA does not find that existing regulations allow for timely review and licensing of MCMs, it should develop additional enabling regulations.

REGULATORY: COACHING AND MENTORING

The FDA needs to augment the resources it currently devotes to technical assistance (i.e., coaching and mentoring) for both government teams and private-sector groups developing MCMs. Developers need to have frequent meetings with the FDA to facilitate development of MCMs, with less bureaucracy. FDA needs to engage with developers throughout the review process, not just at set time points with cumbersome meeting requirements.

Laudably, FDA has been participating in the www.medicalcountermeasures.gov portal. Most requests for meetings with FDA received at that portal also involved requests to meet with other HHS agencies. When the portal went live, FDA received an average of two to five requests per month. The learning curve for the tool was steep for both sponsors and FDA. Recently, one to two requests have arrived each month. Sponsors have requested meetings for a variety of products covering the full range of products FDA regulates. The portal helps FDA understand MCM development work in the private sector and provides guidance to sponsors preparing to meet with FDA.

FDA technical staff (not those with review responsibilities) should be willing to visit MCM developers, when appropriate, as has been done both in the past and recently with other medical products of public-health importance.⁷² FDA needs to clarify its rules on allowed contacts with developers, because practice over the years has led to a more restrictive situation than is useful for important communication.

⁷² Marcus AD. Push to cure rare diseases: FDA officials go to new lengths to encourage applications for orphan-drug status. *Wall Street J*, online edition, March 10, 2010.

Because FDA has effectively become an arbiter of contract compliance for MCM development, FDA-industry communications are essential. Delayed communication between BARDA, FDA and industry can create program delay, introduce uncertainty and hamper program-management efforts. BARDA procurement contracts for products not yet licensed have included multiple objectives and requirements that depend on FDA concurrence or approval (e.g., data needed to support future EUA assessments). Fulfilling FDA requirements and expectations directly affects a contractor's ability to deliver materials to the SNS and subsequently invoice the U.S. Government.

Pay Attention to Clinical Diagnostics

Few tests are FDA-cleared specifically for identification or detection of CBRN threat agents from human samples, and even if such tests are available, relatively few clinical laboratories maintain the trained and experienced personnel and necessary facilities and equipment to provide advanced laboratory testing capability. Public health and LRN laboratories need resources to maintain a core capability for identification of CBRN agents when clinical suspicions arise. This capability could be amplified by permitting other competent clinical laboratories to utilize tests developed and implemented by public health laboratories and/or the LRN, and would enhance patient care.

Many clinical laboratories close to clinical care facilities have insufficient resources to perform any but simple laboratory testing procedures, using diagnostic test products that are FDA-cleared, but waived under the Clinical Laboratory Improvement Amendments (CLIA).⁷³ FDA regulates the reagents, instruments, and systems, and current FDA policy defines a diagnostic test as the set of all system components used. This policy limits laboratory practice options.

In the case of the 2009-10 influenza A/H1N1 pandemic, concerns arose that the restriction on use of the CDC-developed H1N1 tests hindered patient care. Clinical laboratories either had to wait for a commercially developed test or develop their own, a costly and inefficient endeavor. It was helpful to clinical laboratories for FDA to issue EUAs on commercially developed diagnostic tests. Test performance needs to be understood and reasonably reliable, especially in an emergency. In the case of A/H1N1, FDA's accelerated EUA process for diagnostic tests provided health authorities and doctors with some assurance of test performance that was otherwise frequently lacking. It would have been more helpful had the EUAs been issued even more rapidly. Commercial tests were not available until fall 2009, months after initial characterization of the pandemic influenza A/H1N1 strain. Had that pandemic or another emergency been more severe, the problems associated with a lack of diagnostic testing in clinical laboratories might have been amplified. FDA processes and approaches for EUAs and regulation of diagnostic tests need to be streamlined in the context of both public health and clinical laboratory functions.

To fulfill public-health or patient-care needs, laboratory tests must get into laboratories. National goals need to include MCM diagnostic tests suitable for clinical settings, not just reference laboratories. Although initial priority is given to the State Public Health Laboratories

⁷³ See www.cms.hhs.gov/clia/

and CDC-qualified laboratories, dissemination of these tests to clinical laboratories capable of utilizing them in a quality manner needs to follow quickly. While the initial EUA-status tests for H1N1 developed by CDC were useful for documenting spread and epidemiology of the virus, the CDC-developed test had little impact on physician treatment and management decisions because of long turn-around times, declinations to test, and other issues. HHS needs to address distribution and necessary training for newly developed diagnostics, including those used under EUA. Streamlining of the EUA or another regulatory process is essential to ensure adequate clinical laboratory capability.

Response to a CBRN incident begins with identifying the nature of the threat. Clinical laboratories are not yet fully ready to provide accurate diagnosis following exposure and/or infection before and during disaster situations. Resources are devoted primarily to provision of diagnostic testing capability, including new diagnostics, to public health and LRN laboratories; this capability has been designed to support primarily public-health needs versus clinical-care needs. There has been relative inattention to distribution of diagnostics (and training on these diagnostics) to laboratories closer to patients, including those clinical laboratories capable of performing highly sophisticated tests.

More integrated response plans need to be written for distribution of diagnostics to clinical laboratories. Similarly, attention needs to be given to using environmental laboratory capacity that is not currently incorporated into the LRN to amplify emergency response capacity for environmental exposures.

Harmonize the Select Agent Regulations

Biosecurity is an essential element of CBRN MCM research, in terms of physical security, pathogen security, and personnel reliability for laboratories that use, possess, or transfer select agents. But it is also a source of complexity and confusion, due to the proliferation of biosecurity requirements imposed by agencies such as CDC, USDA, DoD, and the U.S. Army.⁷⁴ In the last several years, CDC and USDA have harmonized their regulations, but compliance with these requirements by private-sector partners could be enhanced if the policies implementing the regulations within federal Departments were more fully harmonized. It is not reasonable for the U.S. Government to seek industry collaboration on MCMs, but then ask partners to deal with different biosecurity regimes, depending on the source of budgetary support for the collaboration.

An example of this complexity is the Select Agent Regulations (SAR), which were promulgated by the Secretaries of HHS and USDA, delegated to CDC and the Animal and Plant Health Inspection Service (APHIS), respectively. The SAR require that each individual and entity that possesses, uses, or transfers biological select agents and toxins (BSAT) must register with CDC/APHIS, and that each registered entity establish and implement safety, security, and incident response plans to facilitate safe and secure activities with BSAT. Furthermore, no

⁷⁴ Select Agent Regulations: 42 CFR Part 73 (HHS); 7 CFR Part 331 (USDA); and 9 CFR Part 121 (USDA). Military Requirements: Army Regulation 50-1 Biological Surety, July 28, 2008.

Army Regulation 190-17, Biological Select Agent and Toxin Security Program, September 2009.

DoD Instruction 5210.89, Minimum Security Safeguards for Biological Select Agent and Toxins, April 2006.

“restricted person,” as defined in the Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 (USA PATRIOT Act), may have access to BSAT. All individuals who require access to BSAT must undergo a Security Risk Assessment conducted by the FBI.

In 2008, governmental and non-governmental groups conducted several studies of the Select Agent Program. A key finding of the Executive Order 13486 Working Group on Strengthening the Biosecurity of the United States⁷⁵ was that certain agencies that either house BSAT research or fund BSAT research programs in academic or industrial settings have varying security policies in addition to SAR. For example, DoD Instruction 5210.89 stipulates a Biological Personnel Reliability Program (BPRP). Participants in the BPRP must meet suitability requirements as documented through background investigations, evaluations by “certifying officials” and a competent medical authority, and report potentially disqualifying information about themselves or colleagues.

Commercial entities such as contract research organizations or industrial partners must adopt these costly measures when they receive funding from DoD for BSAT work. Not all funding agencies require such BPRP, but they may perform their own inspections, in addition to CDC/APHIS inspections, with different interpretations of compliance with the SAR, for example, requiring inventory procedures or physical security with costs far exceeding resources granted.⁷⁶ This complication, cost, and frustration particularly affect entities in the earliest stages of MCM development, when live agents or toxins must be used for discovery of potential treatment mechanisms. Training among various funding agencies need to be coordinated so that entities have a single policy to follow, with clear guidelines for resolving any conflict with funding agencies. To set hurdles at this early stage is of great concern. The Board understands that further work toward harmonization is underway and encourages a speedy conclusion to that effort.

Address Product Liability and Injury Compensation

The Public Readiness and Emergency Preparedness (PREP) Act authorizes the Secretary of HHS to issue a declaration that provides immunity from tort liability (except for willful misconduct) for claims of loss relating to administration or use of countermeasures to diseases, threats and conditions determined by the Secretary to constitute a present or credible risk of a future public health emergency to entities and individuals involved in the development, manufacture, testing, distribution, administration, and use of such countermeasures.⁷⁷ A countermeasure covered under a PREP Act declaration may be:

- A qualified pandemic or epidemic product;
- A security countermeasure; or

⁷⁵ Executive Order 13486 Working Group report. See www.hhs.gov/aspr/omsph/biosecurity/biosecurity-report.pdf

⁷⁶ Responsible Research with Biological Select Agents and Toxins. 2009 National Research Council. www.nap.edu/openbook.php?record_id=12774&page=129

⁷⁷ PL 109-148, Dec 30, 2005, www.pandemicflu.gov/plan/federal/prep_act.html. PHS Act Section 319F-3; Section 319F-4, 42 USC 247d-6e. See also Support Anti-terrorism by Fostering Effective Technologies [SAFE-T] Act, within the Homeland Security Act of 2002, PL 107-296.

- A covered countermeasure (e.g., an unapproved drug, biological product, or device authorized for use under an EUA).⁷⁸

These categories include products that are approved, cleared, or licensed under the Federal Food, Drug, and Cosmetic Act (FFDCA) or the Public Health Service (PHS) Act, authorized for investigational use under the FFDCA, or authorized under an EUA under the FFDCA.

The PREP Act authorizes a compensation fund to provide timely, uniform and adequate compensation to eligible individuals for covered injuries directly caused by the administration or use of a covered countermeasure. The Countermeasures Injury Compensation Program (CICP), within HHS's Health Resources and Services Administration (HRSA), has been delegated the responsibility to manage this program. Initial funding to implement the pandemic influenza A/H1N1 portion of CICP (but not anthrax, smallpox, botulism, or radiation syndrome MCMs) was provided to CICP in September 2009 from the pandemic influenza emergency supplemental appropriation of June 24, 2009. CICP needs adequate funding authority imminently for both administrative costs to implement and to maintain the necessary programmatic infrastructure to process claims. It also needs adequate multi-year funding authority to provide adequate and fair compensation for all eligible serious MCM injury claims.

An area where the PREP Act needs statutory revision is the current 1-year filing deadline from time of MCM receipt to filing a request for benefits. Such a short interval led to late filings in a similar program for injury related to smallpox vaccination in 2003. To make the filing deadlines consistent with the National Vaccine Injury Compensation Program, the 1-year filing deadline needs to be increased to the standard 3-year filing deadline.

Regulations to implement the CICP are currently under HHS review. The CICP currently covers pandemic influenza countermeasures such as vaccines, antiviral medications, respiratory protective devices, respiratory support devices, and pandemic influenza diagnostics used to identify, prevent, or treat pandemic influenza. The CICP also covers any authorized vaccine, antimicrobial/antibiotic, other drug or antitoxin, diagnostic, or device to identify, prevent, or treat anthrax, botulism, smallpox, and acute radiation syndrome, but no funding has yet been appropriated for these purposes. Publication of this regulation will permit processing and payment of requests for compensation. Until the regulation becomes final, people may submit "letters of intent" to meet the 1-year filing deadline.⁷⁹

To remove a disincentive to MCM development, immunity from tort liability needs to be provided via a PREP Act declaration issued as part of procurement. This is especially important for MCMs that have other medical uses. PREP Act expressly preempts State and local law and regulations in regard to both tort liability and requirements of the FFDCA for actions taken in accordance with PREP Act declarations.

The lessons learned from the 2009-10 influenza A/H1N1 pandemic (including use of both vaccines and antiviral medications for infants, children, and adults) need to be assessed with regard to the performance of product liability and injury compensation issues for manufacturers,

⁷⁸ Sec 546 of the FFDCA, 21USC 360bbb-3

⁷⁹ Countermeasures Injury Compensation Program, see: www.hrsa.gov/countermeasurescomp

healthcare workers, and product recipients. If modifications to provisions of the PHS Act or the PREP Act are needed, they should be pursued vigorously.

Improve Acquisition Practices

In obtaining MCMs from industrial manufacturers, HHS needs to continue to adopt best practices from the acquisition experience of DoD, DHS, and other federal Departments (e.g., disciplined processes, technology-transition agreements, milestone decision-making process, competitive prototyping, online training via Defense Acquisition University⁸⁰) and from industrial processes (e.g., portfolio management, candidate prioritization).

At the MCM WG workshop and in other forums, Board members heard concerns and frustrations from industry about timeliness of publishing requests for proposal (RFPs), length of MCM review cycles (e.g., "funds in November, big picture in May, decisions in July, contract signed in September"), uncertainty over procurement sizes, contract awards, and approval delays. Other concerns involved inconsistencies among contracting officers, some of whom are viewed as enabling and some as obstructing collaboration.

Primary federal contracting concerns, in general, include risk aversion, equal competitive access, and accountability that make it difficult to execute the responsibilities of the PHEMCE. The advanced development of new products is inherently a riskier process than acquiring a known product with fixed functionalities, and requires additional judgment as to likelihood of developmental success. MCM development is not as amenable to the "fair and open" competition structure as other products (e.g., commodities). BARDA has used the expedited-review process authority to advantage, but it has still been quite slow and conservative in decision making.

The contracting models available for BARDA to choose from are sufficient. They can meet the strategic needs. They can be accountable. The challenge is in bringing about change in the contracting culture to accept that this is a special arena characterized by increased risk, frequent failure during development, and the need to work through issues with contractors collaboratively rather than in confrontation.

HHS should also continue to develop its technology-readiness levels for manufacturing. Manufacturing-readiness levels provide additional detail and clarity for evaluating a candidate product's maturity from the perspective of scale-up and manufacturing in accordance with FDA requirements for current Good Manufacturing Practices (GMPs).

Enhance EUA Preparation

By their nature, CBRN attacks are unpredictable. But some scenarios can be anticipated. Because CBRN incidents may arise before a corresponding MCM is licensed, issues like the use of EUAs need to be made as quick and seamless as possible, by preparing EUA documents

⁸⁰ Defense Acquisition University, www.dau.mil

before a situation begins.⁸¹ For example, rather than wait until a CBRN incident occurs to assemble the scientific data needed by the FDA to issue an EUA,⁸² the PHEMCE needs to do a better job of assembling additional mockup pre-EUA dossiers (including draft patient fact sheets) and data sets. This would be most important for the unlicensed or unapproved MCMs most likely to be needed or whose availability would be most valuable to society. An alternative approach is to encourage commercial MCM sponsors to maintain some pre-EUA dossiers. These dossiers should not be considered mere collections of paper. The American people deserve a thorough, considered review of the medical literature, rather than a pressured and partial review as a crisis unfolds. ASPR needs to reenergize the Secretary's EUA Working Group for this purpose.

Enhance Distribution and Dispensing

A frequent observation is that effective deployment of MCMs comes down to the last mile, actually getting the product to the individual who needs it, in time to provide benefit. MCMs must reach their intended recipients, and reach them promptly, or they are useless.⁸³

The generally successful distribution and dispensing of influenza A/H1N1 vaccine during 2009-10 relied mainly on existing networks of vaccine providers registered with the Vaccines For Children (VFC) program operated by the pharmaceutical wholesaler McKesson Corporation. This list of providers was augmented with additional clinical partners, including the pre-registration of clinicians willing to offer influenza A/H1N1 vaccine. The Tennessee Commissioner of Public Health cited the value of community pharmacies as vaccination sites and as forward distribution points for oseltamivir, including in rural areas. Distribution of influenza A/H1N1 vaccine through the VFC vaccine-distribution system is widely regarded as a success.

The general lesson here may be that scaling up existing systems is better than trying to create systems anew. Users are already familiar with existing systems, which have the capacity to inform and serve priority groups and monitor program effectiveness. Other examples of systems scaled up for the 2009-10 pandemic include the public-health laboratory system, the national adverse-event monitoring system, and disease-surveillance systems.

Many of the specific examples above apply to influenza and are only somewhat applicable to CBRN incidents. Influenza vaccination is an annual ritual for tens of millions of Americans, so the issues arising with vaccination for an unexpected pandemic influenza strain are substantially

⁸¹ 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 information see FDA website, at www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

⁸² FDA Guidance: Emergency Use Authorization of Medical Products, July 2007. www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm. Nightingale SL, Prasher JM, Simonson S. Emergency Use Authorization (EUA) to enable use of needed products in civilian and military emergencies, United States. *Emerg Infect Dis* 2007;13:1046-51. www.cdc.gov/eid/content/13/7/pdfs/vol13no07.pdf

⁸³ Institute of Medicine. Dispensing Medical Countermeasures for Public Health Emergencies: Workshop Summary, 2008. www.nap.edu/catalog/12221.html

less than will arise if the Nation faces an entirely novel disease or hostile CBRN threat requiring unfamiliar medical treatment. And the 2009-10 pandemic unfolded over months, rather than days or hours. Nonetheless, the principle of emphasizing everyday systems is a valuable one across a wide variety of scenarios.

Planning efforts for distribution and dispensing plans must cultivate and maintain strong links to the Nation's public-health and emergency-response systems, recognizing that these systems are ultimately the means by which the PHEMCE will deliver MCMs to the population. In particular, state and local public health agencies have hard-earned experience in reaching out to and communicating with the populations they serve. In a situation where resources may be scarce or supply and demand out of balance, state and local authorities must have some freedom to balance overall federal guidance on distribution and dispensing with their specific knowledge of local needs.

Experience with the influenza A/H1N1 vaccine also showed areas needing improvement. Complication in dispensing arose because the vaccine came in various combinations of formulations and packaging, each with its own label, instructions, and approved age ranges. Similarly, N95 respirators in the SNS came in numerous models and sizes, creating challenges in distribution. Better advance planning and coordination could reduce, if not eliminate, these problems.

Further, while considerable progress was made in creating the CDC dashboard for nationally tracking selected items in the commercial supply chain, there was insufficient detail to give state or local officials information to enable better decisions on when government-owned material should be released. There was no common operating picture to share among the stakeholders in terms of disease levels and supply levels.

The scenarios cited above provide ample reason to encourage greater use of electronic health records and notification systems. Nonintrusive yet accurate and secure means to track patients between care providers need to be incorporated into response plans, to improve patient care and a comprehensive record of care.

Once a particular threat has been identified, challenges remain in assuring readiness to quickly distribute large quantities of appropriate MCMs to local and state emergency managers, and then administer them to people in need. More planning and exercises are needed, along with feedback on optimizing delivery and administration in the field, to continue to address identified weaknesses and specific at-risk populations. To gain realistic experience, it is important to conduct "no notice" or "low notice" exercises. The ASPR needs to explore policy and procedure revisions warranted by federal, state, and local response during the 2009-10 influenza A/H1N1 pandemic, such as engaging more partners who have everyday forms of contact with the public (e.g., health departments, community pharmacies, nongovernmental organizations, entities that prioritize special needs and vulnerable populations). It is unrealistic for health departments, on their own, to be expected to provide successful, timely distribution of MCMs. Many partners will be needed.

HHS needs to determine an appropriate mix of centralized stockpiling (e.g., in the SNS) with prompt distribution to the public by various means (e.g., local distribution sites, or through the U.S. Postal Service (USPS)), and other strategies including household storage of MCMs in packaging such as MedKits and local metropolitan storage, such as with ChemPacks.

It may be reasonable to make licensed vaccines against CBRN threats available to members of the public who prefer primary prevention and have been educated in the risks and benefits of the products. In February 2009, the Advisory Committee on Immunization Practices recognized the utility of offering anthrax vaccine to first responders before a spore release.⁸⁴

A recent Executive Order directs HHS and DoD to develop dispensing plans using the USPS,⁸⁵ but many aspects of distribution and dispensing remain uncertain. Dispensing of MCMs that are prescription drugs by postal workers or state or federal employees could violate section 503(b) of the FDCA. An EUA may be needed to carry out plans incorporating dispensing by such personnel, and some state laws may provide mechanisms to allow dispensing by such personnel. Development of plans for distribution and dispensing of MCMs must also be supported in a way commensurate with the anticipated production levels of MCMs and the needs of and probable risks to the population. Experience shows that a single approach for MCM distribution is unlikely to be adequate. Multiple approaches must be developed, with the best approach for any incident depending on the location and nature of the incident and on the local environment (e.g., metropolitan area vs. rural countryside). Also, different population groups may require multiple approaches for timely distribution of MCMs to be successful. Planning for these multiple approaches needs to involve HHS, DHS, and DoD at the federal level, working closely with regional, state, local and private partners. Funding and exercise of these efforts needs to be at a regional level, because many of these incidents will not be constrained by local or state boundaries.

For many of the EUAs recently issued that authorize an “unapproved use” of a product, the product actually is approved for the indication for which it is being authorized. Unfortunately, there are aspects of the “intended use” of the product during an emergency response that are not part of the product’s approval, licensure, or clearance, and these aspects render the product “unapproved” (and not considered a covered MCM under the PREP Act, unless the product is used under an EUA or an IND protocol). For example, oseltamivir and zanamivir are approved to treat or prevent influenza A infection. However, as part of the response to the influenza A/H1N1 pandemic of 2009-10, EUAs were needed for “unapproved uses” necessary for the emergency use of the product, “uses” for which FDA historically may have exercised its enforcement discretion under emergency circumstances but which would not have been afforded liability protection under the PREP Act. Examples of such “unapproved uses” include the provision of information about emergency distribution not in the approved labeling, omissions in the product label of statutorily required information, deviations from current Good Manufacturing Practices (e.g., extensions of expiry dating), dosing for children younger than 1 year old, use for hospitalized patients, or other situations. FDA may also waive or limit current

⁸⁴ ACIP provisional recommendations for use of anthrax vaccine adsorbed. See www.cdc.gov/vaccines/recs/provisional/downloads/anthrax-vax-Oct2009-508.pdf

⁸⁵ Executive Order 13527. Establishing federal capacity for the timely provision of medical countermeasures following a biological attack, December 30, 2009. *Fed Reg* 2010;75(Jan 6):737-8.

GMP requirements (e.g., limited waiver of GMP with regard to storage conditions, to allow for limited temperature excursions during shipping and storage).

While the Board may follow the fine legal rationale for invoking an EUA under circumstances described above, we encourage regulatory or legislative changes that simplify the situation. The ultimate goal of saving life and limb in an emergency must be kept in mind, and sources of delay must be minimized to the greatest extent possible. Assumptions that normal standards of care can be implemented during a mass-casualty event may not be realized.

More integrated response plans need to be written, similar to those already on the shelf for smallpox and pandemic influenza. These efforts need to be coordinated through the White House, as with the national pandemic influenza plan. The HHS Pandemic Influenza Implementation Plan of 2006 is noteworthy for its detail, metrics, and timetable.⁸⁶ To simplify the task, categorical integrated response plans could perhaps be written for chemical, radiological, contagious infectious disease, and noncontagious infectious-disease scenarios, rather than writing a separate integrated response plan for each material threat agent. These preparatory activities would allow for a quicker, more complete, and better coordinated response, decreasing the time needed for dispensing activities. Not to prepare in these ways runs the risk of wasting time and lives when attacks strike. The Board is troubled by the potential failure of the entire PHEMCE effort by the inability to deliver a necessary MCM to the necessary individuals in a timely manner.

In developing the MCM priorities mentioned above, planners must take into account the logistical and pragmatic needs of healthcare workers who may administer MCMs and the people who will receive them (e.g., refrigerator or freezer space, intravenous injection or infusion, complex patient instructions). For some scenarios it may be technically feasible to lessen the need for medical expertise during CBRN incidents, if MCMs can be provided in oral dosage forms (i.e., tablets, capsules, liquids) or patches, rather than as injections. Developing products that do not require refrigeration would simplify distribution tasks considerably. Almost 20% of the US population reports having a disability (i.e., difficulty seeing, hearing, speaking, lifting/carrying using stairs, walking, grasping small objects),⁸⁷ so dispensing plans need to take into account those with mobility impairments, dependency on others, and other factors that would challenge an equitable dispensing process.

Another dimension of planning is that during a response, there needs to be appropriate surveillance for adherence to MCM instructions, occurrence of adverse events, and evaluation of MCM effectiveness. This surveillance will allow for real-time modifications to the recommended use of the MCM.

This report has focused more on MCM development and deployment than on non-MCM related aspects of emergency response (e.g., hospital preparedness) and recovery (e.g., decontamination). It may be worthwhile for the Secretary or the ASPR to provide targeted questions about such elements of effective response that a new NBSB working group could assess.

⁸⁶ HHS Pandemic Influenza Implementation Plan, November 2006, www.hhs.gov/pandemicflu/implementationplan/

⁸⁷ U.S. Census Bureau. Americans with Disabilities: 2005. www.census.gov/prod/2008pubs/p70-117.pdf

If MCMs could be delivered to each of America's 3,100-plus counties, then there may be 3,100-plus states of readiness across those communities. But it would nonetheless be important for State Governors to give a frank assessment of local readiness to their constituents.

While attending to MCMs that do not yet exist, it will be important for HHS leaders to consider somewhat routine medications and patient teaching. For example, in a nuclear or other blast event, the number of burn injuries may predominate, so attention needs to be paid to burn and antibiotic creams and dressings, and to teaching people how to debride wounds and apply these items.

HHS should continue its international dialogue with the Global Health Security Initiative. HHS should consider engaging Israel to learn lessons about integrating preparedness efforts into everyday healthcare systems.⁸⁸

In a recent report of a workshop on MCM dispensing, the IOM listed many gaps and challenges that remain today (Table 3). This workshop summary also identified several suggestions for improving current planning efforts that need to be carefully evaluated by HHS and DHS (Table 4).⁸⁹

⁸⁸ Association of State and Territorial Health Officials. Public Health Preparedness Infrastructure: Comparing Israel to the United States. Arlington, VA, September 2007.

⁸⁹ Institute of Medicine. Dispensing Medical Countermeasures for Public Health Emergencies: Workshop Summary, 2008. www.nap.edu/catalog/12221.html

Table 3. Institute of Medicine Workshop: Potential Gaps and Challenges in Current Methods of Dispensing Medical Countermeasures *

- **Workforce:** Labor requirements for points of dispensing (PODs) require many personnel.
- **High-touch activity:** Each person who receives medications from PODs must have several time-consuming interactions with POD staff.
- **Need for volunteer training:** Volunteers need training before an event, as well as guidance during an event.
- **Need for medical surveillance for volunteers:** Assurance is needed that volunteers remain healthy during POD operations.
- **Security needs:** Crowds must be controlled to maintain order within and near POD facilities.
- **Patient tracking/registries:** Systems are needed to account for all persons served at PODs.
- **Rapid time frame:** Optimally, PODs would dispense MCMs to a large population within 48 hours of the decision to start dispensing.
- **Lack of coordination among agencies in community:** Often communication and coordination are lacking within various sectors of the community.
- **Lack of framework:** A framework to engage private-sector templates and tools is not available to guide private-sector engagement.
- **Liability issues:** Private-sector volunteers and entities would need protection against liability to participate in the care of others.
- **Leadership:** In some jurisdictions, bioterrorism preparedness is not a top priority and therefore no one is assigned to lead activities if an event occurs.

Table 4. Institute of Medicine Workshop: Ideas for Improving Current Planning Efforts *

- Create innovative frameworks, models, and partnerships for the public and private sectors to meet the massive challenge of dispensing countermeasures to affected populations within 48 hours of the decision to do so.
- Streamline the design of points of dispensing (PODs) to vastly increase the number of people who receive countermeasures in the quickest possible time.
- Cultivate novel alternative POD designs, especially through public–private partnerships for numerous functions, including reduced pressure on public PODs.
- Harness technology systems to track and register people who receive medicines and their lot numbers.
- Identify in advance those at risk for adverse effects from a given countermeasure.
- Ensure liability protection for private-sector partners to distribute and dispense countermeasures.
- Recruit a large workforce, train them, and ensure back-up to fill in if the regular workforce is inadequate or unavailable during an emergency.
- Perform actual planning exercises that permit and encourage improvised decision making.
- Identify the best methods of communication during a public health emergency as well as where and how to obtain medical countermeasures.
- Provide security at PODs and other dispensing sites.

* Adapted from: Institute of Medicine. Dispensing Medical Countermeasures for Public Health Emergencies: Workshop Summary, 2008. www.nap.edu/catalog/12221.html

Take Care of the Children

As America develops a comprehensive MCM program, the Nation must address our children, children with special needs, pregnant women, and others with chronic health conditions. Approximately 25% of the American population is younger than 18 years of age; almost 14% is younger than 10 years of age.⁹⁰ Young people are not a small population to be accorded special treatment, rather they represent a major proportion of the people needing MCMs. A particular weakness of current preparations is lack of information on proper pediatric dosing for the majority of existing MCMs (Table 5). Consequential scenarios include the potential exposure of children to anthrax spores; therefore, the U.S. Government needs to undertake clinical trials to determine the appropriate pediatric dosing of anthrax vaccine. Likewise, HHS should commission clinical studies to determine proper doses of various MCMs for children.⁹¹ The limited amount of data available today is summarized in Table 5. Eventually, HHS should consider developing juvenile and pregnant animal models of effectiveness.

In addition, HHS needs to develop a strategy and implementation plan and identify resources needed to stockpile appropriate quantities of pediatric doses, ideally pre-packaged and stored in the Strategic National Stockpile (SNS). By one estimate, several billion dollars would be needed simply to purchase liquid formulations of antibiotics. With regard to MCM dispensing, it will be important to take into account children with special needs and chronic health conditions, as well as pregnant women.

Furthermore, the U.S. Government needs to assess appropriate device and diagnostic approaches for children. Respiratory-protective devices (e.g., masks, respirators) for children are critical needs. Specimen collection methods are different; one size swab does not fit all. Samples obtained by the most convenient methods must be distinguished from the sampling method that best identifies the disease syndrome. In addition, many diseases may manifest differently in children and require special diagnostic procedures.

⁹⁰ U.S. Census Bureau. www.census.gov/population/socdemo/foreign/pp1-176/tab01-1.pdf

⁹¹ Such studies must be conducted under 21 CFR 50.53 or 50.54, Subpart D, Additional Safeguards for Children in Clinical Investigations.

Table 5. Pediatric Aspects of Top-Priority Medical Countermeasures Against Chemical, Biological, Radiological, and Nuclear Threats

	Vaccine	Antitoxin	Antibiotic or Antiviral Agent(s)	Antidotes and Related Agents	Acute & Delayed Effects of Radiation
Anthrax	C	D	A,B		
Botulism	D	A,C			
Filoviruses (Ebola, Marburg)	D		D		
Glanders, Melioidosis			A		
Junín virus			D		
Plague	D		B		
Smallpox	B		D	C	
Tularemia			B		
Typhus			B		
Radiological or nuclear threats				A,C	E
Volatile nerve agents				A,B,C	

- A – MCM(s) licensed or approved by use in children. Examples: Selected antibiotics, botulism immune globulin intravenous (types A and B), atropine, potassium iodide (KI), Prussian blue (i.e., iron(II,III) hexacyanoferrate(II,III)), injectable calcium-DTPA (i.e., diethylenetriamine pentaacetate) and zinc-DTPA
- B – MCM(s) licensed or approved for adults, but not for children, although pediatric dosing information is available in medical literature. Examples: Selected antibiotics, ACAM2000 smallpox vaccine, midazolam, hydroxocobalamin
- C – MCM(s) licensed or approved for adults, but no pediatric dosing information is available. Examples: Anthrax vaccine adsorbed, Vaccinia immune globulin, pralidoxime (2-pam chloride), nebulized calcium-DTPA and zinc-DTPA
- D – Candidate MCM(s) in development, and pediatric dosing information is limited or not available. Examples: Anthrax antitoxins, botulinum toxoid, heptavalent botulinum antitoxin (types A-G)
- E – Granulocyte-colony stimulating factor (available for use under emergency IND)

Address Functional Needs of At-Risk Individuals

A variety of at-risk populations need special attention before, during, and after a CBRN incident. Almost 19% of the American population in 2005 had a disability, including 7% of the population older than 15 years of age who had difficulty with cognitive, mental, or emotional functioning.⁹² People living in group quarters or institutionalized settings, as well as children and adults with functional needs in the areas of communication (e.g., sensory disabilities, visual disabilities, cognitive disabilities, limited English proficiency) need timely access to MCMs in customized ways.

Members of at-risk populations may have additional needs in one or more of the following functional areas: communication, medical care, maintaining independence, supervision, and transportation. Individuals with underlying disabilities or chronic health conditions and pregnant women may have particular vulnerabilities that must be considered when developing MCMs. These vulnerabilities include how they respond to the toxic agent and how they respond to potential countermeasures. Development incentives, approval processes, and distribution and dispensing plans needs to address at-risk individuals.

For example, during the 2009-10 influenza A/H1N1 pandemic, children and adults with disabilities and chronic health conditions were at risk for additional complications associated with influenza A/H1N1. People with neurological disorders (epilepsy, cerebral palsy, brain or spinal cord injuries, moderate to profound intellectual disability or developmental delay) or neuromuscular disorders (multiple sclerosis or muscular dystrophy), blood disorders, weakened immune systems and chronic lung disorder (asthma) were specifically cited as members of high-risk groups who were eligible for the first increments of vaccine as they became available.

HHS and its local, State, and tribal partners need to develop strategies to reach populations who may be resistant to accepting MCMs (e.g. groups of lower socio-economic status, minority populations, new immigrants, groups that traditionally distrust government). These strategies also need to provide for multiple languages other than English.

Other Preparedness Issues and Observations

The MCM research, acquisition, and fielding issues are so important that they need to be key components of an HHS balanced scorecard or similar management tools. A balanced scorecard is a strategic planning and management system used to align business activities to the vision and strategy of the organization, improve internal and external communications, and monitor organizational performance against strategic goals. Another approach is to develop a responsibility-assignment matrix to identify which players have roles for responsibility, accountability, consultation, or information.⁹³

NBSB members heard PHEMCE stakeholders assert that testing facilities for large-scale animal challenge experiments are insufficient. This issue cuts across multiple Departments and agencies and needs to be addressed in a joint manner. While we have not assessed this situation in the

⁹² U.S. Census Bureau. Americans with Disabilities: 2005. www.census.gov/prod/2008pubs/p70-117.pdf

⁹³ For example, see www.balancedscorecard.org/ and en.wikipedia.org/wiki/Responsibility_assignment_matrix

course of this work, the U.S. Government needs to assess its capacity to perform FDA-required development testing at biosafety levels 3 and 4.

To support the quality and regulatory aspects of MCM development, product developers, BARDA, FDA, and other PHEMCE stakeholders need to expand their collaboration with metrology scientists at the National Institute of Science and Technology (NIST) on standards, reference methods, materials, and data. The importance of measurement accuracy (the closeness of a result to the true value), in contrast to mere repeatability (getting the same result with repeated measurements), cannot be overemphasized. Insufficient accuracy increases the rate of false-positive and false-negative results, impairing scientists' ability to compare results over time and between sites. This is especially important when performing multiplex measurements (e.g., DNA microarrays that assess activity of multiple genes simultaneously), where the measurement result is a complex combination of signals from multiple assays. Examples of prior fruitful collaborations between NIST and various product developers, NIH, and FDA include improved quality of measurement data in laboratory medicine and medical imaging, improved accuracy and reliability of mass spectrometry-based serum proteomic measurements, and improved RNA quantitative measurements. Currently, NIST, the biotechnology industry, and FDA are collaborating on development of new measurement science, reference methods and certified reference materials to facilitate more efficient biologic drug manufacturing and more rapid regulatory approval.

Although the NBSB charge for this review primarily involved human health, the Board notes the importance of preparedness against CBRN threats that may affect agriculture and the environment. Several of the biological threats involve zoonotic diseases (e.g., influenza A/H5N1, anthrax, Rift Valley fever, tuberculosis, brucellosis) that have some overlap with public health. But intentional or emerging threats involving diseases of plants or animals (e.g., foot and mouth disease) also need considerable federal attention related to food safety and security and preserving economic value. The federal efforts include exclusion, prevention, surveillance, detection, response, decontamination, and recovery activities. Countermeasure activities could parallel the PHEMCE. Environmental concerns include areas of human habitat, wetlands, and other special ecosystems. The issues involve arthropod-vector control, health of wildlife, decontamination and adverse effects of interventions (e.g., insecticides) on ecosystems. The Board urges the U.S. Government to prioritize efforts to prepare for, respond to, and mitigate the agricultural and environmental effects of CBRN agents.

Recommendations:

- 14. The ASPR promptly provides a plan to the Secretary of HHS to provide for centralized advanced development and manufacturing of selected biological MCMs, based on one or more public-private partnerships (PPPs) or federally funded research-and-development centers. (FFRDCs).**
- 15. The FDA Commissioner promptly provides a plan to the Secretary of HHS for designating appropriate candidate MCMs for high-priority review, with the appropriate criteria of evidence for safety and efficacy.**
- 16. The FDA Commissioner promptly advises the Secretary of HHS on a plan to revise the draft guidance on the "animal rule."**

17. The CDC, BARDA, and NIAID Directors develop a plan for the ASPR for identifying and addressing the need for screening and diagnostic tests for CBRN agents that can be performed in clinical settings, prioritized among other MCM needs.
18. The ASPR, in coordination with leaders of other relevant agencies:
 - A. Identifies to the Secretary of HHS needs for additional pediatric products for the SNS.
 - B. Provides to the Secretary of HHS a plan to determine pediatric dosages for at least three MCMs.
 - C. Identifies to the Secretary of HHS a plan to create and maintain pre-Emergency Use Authorization (EUA) dossiers for the top 20 MCMs, in coordination with DoD.
 - D. Provides to the Secretary of HHS a plan to write integrated response plans for three high-priority threat scenarios, to describe response from alert to MCM dispensing.
 - E. Provides to the Secretary of HHS an evaluation of State-level MCM distribution plans to assess adequacy in caring for children and for individuals with functional limitations, and a plan to resolve common problems identified.
19. The NIH Director and NIAID Director provide the Secretary of HHS a plan on how to align NIH resources for MCMs to the national prioritized lists of research goals and product requirements.
20. The Secretary of HHS (working with NIH, NIAID, BARDA, and DoD) develops a plan to rationally allocate limited animal resources and facilities to CBRN animal-model development and testing in alignment with the national prioritized list of research goals.
21. The Secretary of HHS develops a plan to fund the CICP for all covered countermeasures, and to extend the filing deadline to a consistent 3-year interval.

Possible Food-Contamination Scenario:

Two kinds of bacteria (e.g., *Salmonella* and *E. coli* O157:H7) intentionally placed into short- and medium-shelf-life foods (e.g., leafy vegetables, hot dogs). Among those who eat these products, ~ 35% become ill.

Community recovery timeline: Weeks

Source: Hartnett E, Paoli GM, Schaffner DW. Modeling the public health system response to a terrorist event in the food supply. *Risk Analysis* 2009;29(Nov):1506-20.

V. Enhanced Communication

Progress in developing and distributing MCMs has been hampered by inadequate communications at many levels. Most fundamentally, perhaps, the U.S. Government has failed to explain to the American people the urgent need for countermeasures to a variety of CBRN threats. The U.S. Government needs to prepare threat and risk assessments suitable for public communication to provide a basis for public engagement on the consequences of CBRN threats. Development of an effective national strategy for MCM development, supported by consistent leadership and funding, has been difficult in an environment in which public awareness of threat spikes following individual events but subsides thereafter.

Experience with the influenza A/H1N1 pandemic also showed considerable variation in the acceptance of the vaccine by members of the public, despite a concerted public information campaign. Public concerns of this sort raise issues much larger than emergency preparedness (e.g., fears about vaccines in general, distrust of medical assistance from the government among populations typically underserved by the health care system), but they must nevertheless be taken into account in plans to dispense MCMs on a large scale or on short notice. Experience from local public-health agencies showed that outreach through trusted figures, including members of the faith-based community and local community-oriented organizations, was valuable in reaching diverse sectors of the population. Imparting information about coping with pandemic influenza to schoolchildren proved effective as a means of informing parents.

CBRN and MCM communications (e.g., explanations of threat, product instructions, dispensing sites public information about assistance) must be accessible to all and communication must be in appropriate alternative formats. Accessibility of information means that websites with visual or audio formats, for example, must include versions of those items meaningful to those with vision or hearing impairment. Alternate information formats include Braille, large print, and electronic storage forms such as compact disk or flash drive. Ensuring information is developed and disseminated in multiple media—and in formats that are multi-lingual, alternative, age-appropriate and user-friendly—is crucial to developing emergency plans for inclusion of at-risk individuals into the mainstream of information sharing on MCMs.

Better communication with the public, especially from state, local, and tribal health authorities, can also lay the groundwork for more effective dispensing and acceptance of MCMs. The U.S. Government should consider the potential role of the U.S. Surgeon General and the Office of Science and Technology Policy to assist in this communication effort, recognizing that local community leaders will be most influential with some sectors of the population. Such efforts need to take into account the needs of those with disabilities and difficulties with standard information delivery channels. Delivery of MCMs through the USPS, for example, should not come as a surprise to the public. Alternately, pre-positioning of MCMs in the form of MedKits, distributed to households, requires clear explanation of their purpose and clear instruction on when and how they should be used.

PHEMCE and ASPR leaders need to think of themselves as leading a very specific type of research and development organization with a distinct primary leader. The primary leader needs

to develop a strategy that brands the PHEMCE so the American public understands the importance of HHS and ASPR as they execute their role in preparedness and response.

Improved communication is also needed at several levels within Government. Additional senior leaders at FDA and other HHS agencies need to apply for security clearances, so they can better understand the nature and consequences of CBRN threats. Medical review teams need to be provided full and appropriate education and training on the consequences of CBRN threats. CDC needs to assess its degree of specificity of communication with State and local preparedness departments, regarding distribution from the SNS, use of EUAs, and other response issues. Appropriate considerations in risk communication and message testing apply.

The U.S. Government needs to develop an unprecedented degree of collaboration with the biopharmaceutical industry. HHS needs to reach out to experienced pharmaceutical companies with explicit requests for support of the national goals.

In a similar manner, the U.S. Government needs to enhance its international collaborative programs, recognizing that some nations have ongoing programs of interest to U.S. efforts, or will want to begin attending to their own people's needs.

Recommendations:

- 22. The ASPR provides to the Secretary of HHS a plan to release more information on CBRN consequences to the public, as part of a sustained multi-faceted education and communication plan.**
- 23. The ASPR provides to the Secretary of HHS a plan to make information about MCMs available to the public before and during emergencies in appropriate, accessible and alternative formats.**

Actual Sarin Scenario:

Incomplete release of liquid sarin on three lines of the Tokyo subway system during rush hour – 12 deaths, ~500 treated at hospital, 5,500 injured, secondary contamination of nursing and medical staff at hospital.

Community recovery timeline: Days to weeks.

Source: Tokuda Y, Kikuchi M, Takahashi O, Stein GH. Prehospital management of sarin nerve gas terrorism in urban settings: 10 years of progress after the Tokyo subway sarin attack. *Resuscitation* 2006;68(Feb):193-202.

Conclusion

Medical countermeasures are and must be a national security priority. The pathway to success must start with a unifying National Strategy provided by the White House.

America's enemies will not issue advance warning that they are about to attack with chemical, biological, radiological, or nuclear weapons. Nature will not provide notice that a new infectious disease is about to emerge. America needs urgent and wisely planned action to counter the grave danger it faces from the range of CBRN threats, whether natural or the result of hostile action.

Progress in the life sciences enables both the creation of new threats as well as development of countermeasures. Given America's current vulnerabilities, U.S. Government efforts to accelerate the MCM program must start now, be vigorous, and continue well into the future. Appropriate discussion of threat consequences will help explain to the American public the importance of addressing CBRN threats.

The Nation must take the initiative in developing safe and effective MCMs to safeguard national security and public health. The ASPR must exercise clear operational leadership. To focus efforts initially, the Secretary of HHS needs to identify and declare the three most important MCMs needed to counter important current vulnerabilities. Licensed MCMs for both children and adults must be added to the U.S. arsenal of defenses as soon as possible.

Successful development of MCMs requires leaders in multiple parts of the U.S. Government to make clear the urgency of the threat and to set clear priorities. During the MCM WG workshop, the ASPR described meeting recently with manufacturing executives who lauded the teamwork, flexibility, and interaction between NIH, BARDA, CDC, and FDA during the 2009-10 pandemic, and then asked why those positive events can't happen more often?

Indeed, it must happen much more often, especially during periods of peace.

America expects orchestration within HHS's scientific endeavors, not cacophony.

HHS leaders must then foster cooperation and collaboration among government, academia, industry, and health authorities. All the stakeholders must work in concert. Past combinations of public and private activity have been insufficient to develop, procure, and field the MCMs America needs. The U.S. Government must employ a variety of creative incentives to bring private industry into the effort, merging the creative spark of biotech companies with the experience and resources of large pharmaceutical firms. Only by harnessing industry's inventiveness and talent can MCMs be produced with the quality, quantity, and urgency needed.

"Preparing for the next public health emergency is a full-time job and we need to do it whether there's another crisis going on or not."

- Kathleen Sebelius, HHS Secretary, December 1, 2009

Within the U.S. Government itself, many agencies with MCM responsibilities will contribute to the effort. Their activities must be integrated far more efficiently than in the past. To harness their full talent, HHS needs to develop synchronized budget requests to meet prioritized research goals, prioritized product requirements, and prioritized dispensing goals. The MCM portfolio must balance all stages of development and fielding, from early research to production and procurement, to acquisition, distribution and public deployment. The FDA must be given the resources it needs to regulate MCMs. The Commissioner needs to acknowledge and act on FDA's implicit national security role in defending America.

Without fail, the overall effort must enhance the plans to distribute MCMs and dispense them to the American people. Those plans must engage from the outset the experience and advice of local partners who will be responsible for the "last mile" of distribution and dispensing.

Consistent, adequate, and balanced funding is essential. Multi-year funding for MCM activities within HHS will not only facilitate consistency in meeting national strategic priorities, but will also build confidence among industrial partners that the government is a dependable partner.

Protecting the Nation against CBRN threats relies on discipline, vigilance, perseverance, determination, and commitment. Public concern as well as government actions typically spike in response to specific events but subside at other times. Better communication by the U.S. Government can help to maintain an appropriate level of concern and action from year to year, regardless of unpredictable events. Ultimately, it is the Government's responsibility to ensure that MCM development is sustained over the many years it will take to reach national goals.

Developing MCMs to the point of practical utility involves technical risk. It demands persistence (even in periods of calm) and courage to refine successful MCMs from the numerous candidate products that will not come to fruition. Planning and leadership will reduce the risks and uncertainties, but cannot erase them. But the risk of doing nothing is greater. The Nation's security depends on undertaking the effort, despite the risks.

The actions listed above require the exercise of vibrant and sustained leadership, and the ongoing cultivation of a productive, collaborative, science-based workforce to make the enterprise thrive. Implementation of this Board's recommendations should result in more persistent, innovative, and fruitful efforts to develop the full portfolio of MCMs needed to protect America against CBRN agents. This effort must be sustained, even in periods of calm, because the road is long and we must have discipline to stay the course.

Leaders matter. Leaders prioritize, set goals, and define the mission. When it comes to medical countermeasures against chemical, biological, radiological, and nuclear threats, including emerging infectious diseases, leaders matter. The vulnerabilities persist until we reach the goals, together.

Medical countermeasures are a matter of national security.

Appendix 1: Recommendations to the U.S. Government

Note: For simplicity, these recommendations typically cite a small number of responsible federal leaders to perform an action. In all such cases, the Board expects and assumes that appropriate coordination within and between Departments and agencies will be conducted.

* designates recommendations the Board considers pivotal (5, 8, 11, 15, 19).

1. The Secretary of HHS, in coordination with Secretaries of Defense and Homeland Security, confers and coordinates with the White House on how best to protect America from CBRN threats, including the merits of establishing a position on the National Security Council (NSC) to lead the relevant National Strategy.
2. The Secretary of HHS, in coordination with Secretaries of Defense and Homeland Security, coordinates with the White House on a unifying end-to-end National Strategy to address intentional, natural, and emerging CBRN threats.
3. The Secretary of HHS promptly identifies at least three high-priority new MCMs that the Department will develop to counter CBRN threats, with target timelines. At least one of these MCMs should address radiation exposure.
4. The Secretary of HHS promptly coordinates with the Secretaries of Defense and DHS and DoD to develop prioritized lists of CBRN threats of both natural and intentional origin, to guide further prioritization of MCM efforts.
5. * The Secretary of HHS empowers the ASPR as the operational MCM leader, with authority to synchronize the efforts of HHS agencies and with end-to-end oversight.
6. The Secretary of HHS tasks the ASPR to refine the HHS acquisition structure and metrics, to provide accountability for the MCM program.
7. The Secretary of HHS designates the Director of the Biomedical Advanced Research and Development Authority (BARDA) as the MCM Portfolio Director, to coordinate technical aspects of balancing the HHS MCM portfolio.
8. * The Secretary of HHS promptly tasks senior HHS leaders to develop a common set of prioritized research goals, prioritized product requirements, and prioritized dispensing goals for civilian populations; and coordinates these priorities with DoD.
9. The Secretary of HHS, in consultation with the Secretary of DHS, develops a plan to overcome existing obstacles that preclude timely distribution and administration of MCMs to people in need (including children and those with limited functional ability).
10. The Secretary of HHS promptly determines the coordinated budget requirements for Fiscal Year (FY) 2011 relevant to CBRN MCM budget lines within National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), BARDA, Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and ASPR (and in conjunction with DoD), and communicates requests for revision of the President's Budget to the Office of Management and Budget. Secretary gives special attention to FDA resource needs.

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11. * For FY2012 and beyond, the Secretary of HHS develops a coordinated budget request relevant to CBRN MCM budget lines within NIH, NIAID, BARDA, CDC, FDA, and ASPR (and in conjunction with DoD).
12. The Secretary of HHS develops a legislative plan to seek multi-year funding authority for CBRN MCM efforts.
13. The Secretary of HHS develops a legislative plan to seek appropriate modification and reauthorization of the Project BioShield Special Reserve Fund, before its expiration in 2013.
14. The ASPR promptly provides a plan to the Secretary of HHS to provide for centralized advanced development and manufacturing of selected biological MCMs, based on one or more public-private partnerships (PPPs) or federally funded research-and-development centers (FFRDCs).
15. * The FDA Commissioner promptly provides a plan to the Secretary of HHS for designating appropriate candidate MCMs for high-priority review, with the appropriate criteria of evidence for safety and efficacy.
16. The FDA Commissioner promptly advises the Secretary of HHS on a plan to revise the draft guidance on the "animal rule."
17. The CDC, BARDA, and NIAID Directors develop a plan for the ASPR for identifying and addressing the need for screening and diagnostic tests for CBRN agents that can be performed in clinical settings, prioritized among other MCM needs.
18. The ASPR, in coordination with leaders of other relevant agencies:
 - A. Identifies to the Secretary of HHS needs for additional pediatric products for the SNS.
 - B. Provides to the Secretary of HHS a plan to determine pediatric dosages for at least three MCMs.
 - C. Identifies to the Secretary of HHS a plan to create and maintain pre-Emergency Use Authorization (EUA) dossiers for the top 20 MCMs, in coordination with DoD.
 - D. Provides to the Secretary of HHS a plan for drafting three concepts of operations for managing to write integrated response plans for three high-priority threat scenarios, to describe response from alert to MCM dispensing.
 - E. Provides to the Secretary of HHS an evaluation of State-level MCM distribution plans to assess adequacy in caring for children and for individuals with functional limitations, and a plan to resolve common problems identified.
19. * The NIH Director and NIAID Director provide the Secretary of HHS a plan on how to align NIH resources for MCMs to the national prioritized lists of research goals and product requirements.
20. The Secretary of HHS (working with NIH, NIAID, BARDA, and DoD) develops a plan to rationally allocate limited animal resources and facilities to CBRN animal-model development and testing in alignment with the national prioritized list of research goals.
21. The Secretary of HHS develops a plan to fund the Countermeasures Injury Compensation Program for all covered countermeasures, and to extend the filing deadline to a consistent 3-year interval.

22. The ASPR provides to the Secretary of HHS a plan to release more information on CBRN consequences to the public, as part of a sustained multi-faceted education and communication plan.
23. The ASPR provides to the Secretary of HHS a plan to make information about MCMs available to the public before and during emergencies in appropriate, accessible and alternative formats.⁹⁴

Pivotal Recommendations

5. The Secretary of HHS empowers the ASPR as the operational MCM leader, with authority to synchronize the efforts of HHS agencies and with end-to-end oversight.
8. The Secretary of HHS promptly tasks senior HHS leaders to develop a common set of prioritized research goals, prioritized product requirements, and prioritized dispensing goals for civilian populations; and coordinates these priorities with DoD.
11. For FY2012 and beyond, the Secretary of HHS develops a coordinated budget request relevant to CBRN MCM budget lines within NIH, NIAID, BARDA, CDC, FDA, and ASPR (and in conjunction with DoD).
15. The FDA Commissioner promptly provides a plan to the Secretary of HHS for designating appropriate candidate MCMs for high-priority review, with the appropriate criteria of evidence for safety and efficacy.
19. The NIH Director and NIAID Director provide the Secretary of HHS a plan on how to align NIH resources for MCMs to the national prioritized lists of research goals and product requirements.

⁹⁴ Accessibility means that websites with visual or audio formats, for example, must include versions of those items meaningful to those with vision or hearing impairment. Alternate information formats include Braille, large print, and electronic storage forms such as compact disk or flash drive.

Appendix 2: Summary of Issues and Solutions

Issue (i.e., "diagnosis")	Solution (i.e., "treatment")
Lack of urgency in national effort to counter CBRN threats	Leadership of effort must begin at the White House, then to senior leaders of HHS, DoD, DHS, and relevant agencies
Lack of coherence on how to organize federal assets to counter the gravest CBRN threats	Establish unified national strategy encompassing all aspects of responsiveness
Lack of prioritization of threats, research goals, product requirements, and dispensing goals	Develop prioritized list of threats and portfolio of urgently needed MCMs
Lack of synchronization and integration of effort among agencies and Departments contributing to MCM development	HHS Secretary needs to assure cooperation across HHS agencies, to adopt shared priorities with appropriate metrics, including coordinated budgets
PHEMCE Enterprise Governance Board does not really govern	Need for ASPR leadership to achieve orchestrated effort by the HHS agencies
Imbalanced MCM portfolio	Develop a rational process to optimize the portfolio of candidate MCM products
Failure to fully engage biotechnological and pharmaceutical industry	Devise menu of incentives for industry participation, and follow through with durable government support
Growing collaboration between DoD and HHS efforts	Encourage and enhance the collaboration
Inadequate acquisition structure	Revise acquisition structure, adopt best practices
Yearly HHS budgeting does not support long-term MCM development	Establish multi-year budgeting for MCM effort within HHS
Inconsistent support as candidate MCMs pass through progressive stages of development and transition from one HHS division to another	HHS agencies must develop transition teams to assure time and resources are not wasted
Inadequate resources	Consistent, adequate, balanced funding from Congress and OMB
FDA inadequately resourced and insufficiently focused on MCM regulatory challenges	Increase FDA funding. FDA to revise regulatory approach and prioritization for MCMs

Summary of Issues and Solutions (continued)

Issue (i.e., "diagnosis")	Solution (i.e., "treatment")
Confusion and frustration over the "animal rule"	Revise current draft guidance to industry, after scientific forum
Inadequate national ability to quickly identify a novel threat	National goals need to include diagnostics suitable for clinical settings, not just reference laboratories
Uncertainty whether MCMs can distributed and dispensed in time to be useful to the people who need them	Resources to allow additional exercising of concepts of operations, in conjunction with state and local health authorities and their partners, for distribution and dispensing
Lack of information on pediatric MCM dosing and treatment; lack of pediatric dosage forms	Determine pediatric needs, and stockpile pediatric MCM dosage forms
Public uncertainty over response to CBRN incident	Improve communication to public, engaging local health officials and other trusted figures

Appendix 3: Selected Portions of the Pandemic and All-Hazards Preparedness Act (PAHPA)⁹⁵

"SEC. 2811. COORDINATION OF PREPAREDNESS FOR AND RESPONSE TO ALL-HAZARDS PUBLIC HEALTH EMERGENCIES.

"(a) IN GENERAL.—There is established within the Department of Health and Human Services the position of the Assistant Secretary for Preparedness and Response. The President, with the advice and consent of the Senate, shall appoint an individual to serve in such position. Such Assistant Secretary shall report to the Secretary.

"(b) DUTIES.—Subject to the authority of the Secretary, the Assistant Secretary for Preparedness and Response shall carry out the following functions:

"(1) LEADERSHIP.—Serve as the principal advisor to the Secretary on all matters related to Federal public health and medical preparedness and response for public health emergencies.

"(2) PERSONNEL.—Register, credential, organize, train, equip, and have the authority to deploy Federal public health and medical personnel under the authority of the Secretary, including the National Disaster Medical System, and coordinate such personnel with the Medical Reserve Corps and the Emergency System for Advance Registration of Volunteer Health Professionals.

"(3) COUNTERMEASURES.—Oversee advanced research, development, and procurement of qualified countermeasures (as defined in section 319F–1) and qualified pandemic or epidemic products (as defined in section 319F–3).

"(4) COORDINATION.—

"(A) FEDERAL INTEGRATION.—Coordinate with relevant Federal officials to ensure integration of Federal preparedness and response activities for public health emergencies.

"(B) STATE, LOCAL, AND TRIBAL INTEGRATION.—Coordinate with State, local, and tribal public health officials, the Emergency Management Assistance Compact, health care systems, and emergency medical service systems to ensure effective integration of Federal public health and medical assets during a public health emergency.

"(C) EMERGENCY MEDICAL SERVICES.—Promote improved emergency medical services medical direction, system integration, research, and uniformity of data collection, treatment protocols, and policies with regard to public health emergencies.

"(5) LOGISTICS.—In coordination with the Secretary of Veterans Affairs, the Secretary of Homeland Security, the General Services Administration, and other public and private entities, provide logistical support for medical and public health aspects of Federal responses to public health emergencies.

"(6) LEADERSHIP.—Provide leadership in international programs, initiatives, and policies that deal with public health and medical emergency preparedness and response.

"(c) FUNCTIONS.—The Assistant Secretary for Preparedness and Response shall—

"(1) have authority over and responsibility for—

"(A) the National Disaster Medical System (in accordance with section 301 of the Pandemic and All-Hazards Preparedness Act); and

"(B) the Hospital Preparedness Cooperative Agreement Program pursuant to section 319C-2;

⁹⁵ 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

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"(2) exercise the responsibilities and authorities of the Secretary with respect to the coordination of—

"(A) the Medical Reserve Corps pursuant to section 2813;

"(B) the Emergency System for Advance Registration of Volunteer Health Professionals pursuant to section 319I;

"(C) the Strategic National Stockpile; and

"(D) the Cities Readiness Initiative; and

"(3) assume other duties as determined appropriate by the Secretary."; and

"(4) by striking "Assistant Secretary for Public Health Emergency Preparedness" each place it appears and inserting "Assistant Secretary for Preparedness and Response".

Appendix 4: Selected CBRN Consequences, Possible and Actual

Possible Anthrax Scenario: Anthrax spores dispersed in a line across an urban area -- 83,000 to 313,000 people infected, ~ 8,000 to 146,000 develop anthrax disease (varies with speed of antibiotic distribution). Square miles of buildings abandoned until they can be decontaminated.

Recovery timeline: Months to years.

Sources:

- Baccam P, Boechler M. Public health response to an anthrax attack: An evaluation of vaccination policy options. *Biosecurity Bioterror* 2007;5:26-34.
- Wein LM, Craft DL. Evaluation of public health interventions for anthrax: A report to the Secretary's Council on Public Health Preparedness. *Biosecurity Bioterror* 2005;3:348-56.

Possible Botulism Scenario: Botulism toxin introduced into milk-processing facility, ~ 100,000 to 568,000 people poisoned, 28% to 99% of whom are children. Perhaps 60% of poisoned individuals would require mechanical ventilation, far surpassing the number of ventilators available. Death rate in large-scale attack could range from 25% to 60%.

Public anxiety over security of milk-distribution system.

Community recovery timeline: Months

Source: Wein LM, Liu Y. Analyzing a bioterror attack on the food supply: The case of botulinum toxin in milk. *Proc Natl Acad Sci USA* 2005;102(Jul 12):9984-9.

Actual Chlorine Scenario: Train derailment discharges up to 70 tons of chlorine – 9 deaths, > 525 injuries, relocation of > 5,000 people for up to 9 days.

Community recovery timeline: Weeks.

Sources:

- Buckley RL, Hunter CH, Addis RP, Parker MJ. Modeling dispersion from toxic gas released after a train collision in Graniteville, SC. *J Air Waste Manag Assoc* 2007;57(Mar):268-78.
- CDC. Public health consequences from hazardous substances acutely released during rail transit—South Carolina, 2005; Selected States, 1999-2004. *MMWR* 2005;54(Jan 28):64-7.

Consider also:

Possible Chlorine Scenario: A bomb detonates under a tractor-trailer tanker carrying compressed liquid chlorine. Depending on weather conditions and population density, 100 to 11,000 hospitalizations, ~ 20 to 700 fatalities.

Community recovery timeline: Weeks.

Source: Scheulen JJ, Thanner MH, Hsu EB, Latimer CK, Brown J, Kelen GD. Electronic Mass Casualty Assessment and Planning Scenarios (EMCAPS): Development and application of computer modeling to selected National Planning Scenarios for high-consequence events. *Ann Emerg Med* 2009;53(Feb):226-32.

Consider also:

Lehavi O, Leiba A, Dahan Y, Schwartz D, Benin-Goren O, Schwartz R, Augarten A, Ben-Ari J, Ben-Yehuda Y, Weiss G, Levi Y, Bar-Dayana Y. Lessons learned from chlorine intoxications in swimming pools: The challenge of pediatric mass toxicological events. *Prehosp Disaster Med* 2008;23(Jan-Feb):90-5.

Possible Radiation Scenarios:

- Radiation-dispersal device (RDD) explodes at busy street corner. ~ 30 to 180 deaths.
- Radiation-exposure device (RED) concealed at high-traffic area. ~ 60 to 250 deaths and ~ 130 cases of radiation sickness needing treatment for 30 years.

Effect on public behavior. Decontamination efforts for people and objects.

Community recovery timeline: Months to years.

Source: Tofani A, Bartolozzi M. Ranking nuclear and radiological terrorism scenarios: The Italian case. *Risk Anal* 2008;28(Oct):1431-44.

Possible Nuclear Scenario: Explosion from improvised nuclear device, 10 tons to 10 kilotons, in center of a city, few hundred to 100,000 deaths, number of hospitalizations not estimated. Economic costs: Trillions of dollars.

Community recovery time: Years

Source: Tofani A, Bartolozzi M. Ranking nuclear and radiological terrorism scenarios: The Italian case. *Risk Anal* 2008;28(Oct):1431-44.

Possible Food-Contamination Scenario: Two kinds of bacteria (e.g., *Salmonella* and *E. coli* O157:H7) intentionally placed into short- and medium-shelf-life foods (e.g., leafy vegetables, hot dogs). Among those who eat these products, ~ 35% become ill.

Community recovery timeline: Weeks

Source: Hartnett E, Paoli GM, Schaffner DW. Modeling the public health system response to a terrorist event in the food supply. *Risk Anal* 2009;29(Nov):1506-20.

Actual Sarin Scenario: Incomplete release of liquid sarin on three lines of the Tokyo subway system during rush hour – 12 deaths, ~500 treated at hospital, 5,500 injured, secondary contamination of nursing and medical staff at hospital.

Community recovery timeline: Days to weeks.

Source: Tokuda Y, Kikuchi M, Takahashi O, Stein GH. Prehospital management of sarin nerve gas terrorism in urban settings: 10 years of progress after the Tokyo subway sarin attack. *Resuscitation* 2006;68(Feb):193-202.

Appendix 5: Roster of the NBSB Medical Countermeasures Working Group

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Appendix 6: Objectives and Roster of MCM Working Group Workshop Attendees

Objectives:

- Identify essential aspects of strategic management of the PHEMCE to be changed or improved.
- Describe current exercise of leadership among PHEMCE stakeholders and identify how best to synchronize HHS agencies toward common goals.
- Identify ways to improve the current accountability structure, so that the Secretary of HHS can effectively accelerate development and fielding of medical countermeasures.
- Describe current funding streams and identify means to improve them.
- Describe current and optimal means of prioritizing MCM endeavors, balancing early and advanced development, chemical-biological-radiological-nuclear, adults and children, diagnosis-prevention-treatment, and other strategic choices.
- Identify key constraints on MCM endeavors and propose means to overcome the constraints.

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Appendix 8: Acronyms and Abbreviations

APHIS	Animal and Plant Health Inspection Service
ASPR	Office of the Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BSAT	Biological Select Agents and Toxins
BPRP	Biological Personnel Reliability Program
CBER	Center for Biologics Evaluation and Research
CBDP	Chemical and Biological Defense Program
CBRN	Chemical, Biological, Radiological, and Nuclear
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CICP	Countermeasures Injury Compensation Program
CLIA	Clinical Laboratory Improvement Amendments
CONOPS	Concepts of Operations
CRADA	Cooperative Research and Development Agreement
DARPA	Defense Advanced Research Projects Agency
DAU	Defense Acquisition University
DHS	U.S. Department of Homeland Security
DoD	U.S. Department of Defense
DTPA	Diethylentriamene pentaacetate
DTRA	Defense Threat Reduction Agency
EEC	Enterprise Executive Committee
EGB	Enterprise Governance Board
EUA	Emergency Use Authorization
FAR	Federal Acquisition Regulations
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetics Act
FFRDC	Federally Funded Research and Development Center
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
HHS	U.S. Department of Health and Human Services
HRSA	Health Resources and Services Administration
HSPD	Homeland Security Presidential Directive
IND	Investigational New Drug
IOM	Institute of Medicine
IP	Intellectual Property
IPT	Integrated Product Team (DoD); Integrated Program Team (HHS)
JBAIDS	Joint Biological Agent Identification and Diagnostic System
JPEO-CBD	Joint Program Executive Office for Chemical/Biological Defense
JRO	Joint Research Office
JSTO	Joint Science and Technology Office
KI	Potassium iodide
LRN	Laboratory Research Network
MCM	Medical Countermeasure

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MDA	Milestone Decision Authority
MTA	Material Threat Assessment
MTD	Material Threat Determination
NIST	National Institute of Standards and Technology
NBSB	National Biodefense Science Board
NHP	Nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NSC	National Security Council
OCET	Office of Counterterrorism and Emerging Threats
OMB	Office of Management and Budget
OPEO	Office of Preparedness and Emergency Operations
PAC	Portfolio Advisory Committee
PAHPA	Pandemic and All-Hazards Preparedness Act
PCT	Product Coordinating Team
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PHS	Public Health Service
PL	Public Law
POD	Point of Dispensing
POM	Program Objective Memorandum
PPP	Public-Private Partnership
PREP Act	Public Readiness and Emergency Preparedness Act
RDD	Radiation-Dispersal Device
RED	Radiation-Exposure Device
RFP	Request for Proposal
SAFE-T	Support Anti-terrorism by Fostering Effective Technologies
SAR	Select Agent Regulations
SNS	Strategic National Stockpile
SRF	Special Reserve Fund
TMTI	Transformational Medical Technologies Initiative
TPP	Target Product Profile
TRL	Technology-Readiness Levels
USC	United States Code
USDA	Department of Agriculture
USPS	U.S. Postal Service
VA	U.S. Department of Veterans Affairs
VFC	Vaccines for Children
VIG	Vaccinia Immune Globulin
WG	Working Group
WMD	Weapons of Mass Destruction