U.S. Department of Health and Human Services
Assistant Secretary for Preparedness and Response

The Public Health Emergency Medical Countermeasures Enterprise Review

Transforming the Enterprise to Meet Long-Range National Needs

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Executive Summary

In his State of the Union Address, President Obama emphasized a key theme for his leadership – "engagement that advances the common security and prosperity of all people." An integral part of this common security and prosperity is safety from bioterrorism and emerging infectious disease threats that can result in significant health consequences. The President further signaled his commitment to ensure our Nation is as prepared as possible for these threats, telling the American people that the U.S. Government would be "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." The National Health Security Strategy (NHSS), released in December 2009, was developed to "galvanize efforts to minimize the health consequences associated with significant health incidents." As part of the emerging strategy to strengthen public health both domestically and abroad, and to increase the Nation's capacity to respond quickly and efficiently to these threats, the NHSS describes ten strategic objectives necessary to achieve a national vision of health security. Among these is the need to promote and sustain an effective medical countermeasures (MCMs) enterprise.

Secretary Sebelius, understanding that the President, Congress, and the American people look to the Department of Health and Human Services (HHS) to ensure that we can protect the nation against such threats, asked for a review of the Department's MCM enterprise with the goal of ensuring that our Nation has a forward-looking, 21st-century system upon which it can rely. HHS recognizes that there are multiple components and organizations critical to the timely development, deployment, and use of MCMs, including critical investment in the Nation's public health system. Indeed, absent the means to detect a health threat or distribute and administer an MCM, investments in the development and manufacturing of MCMs are of limited value. While recognizing these important dependencies, this review is limited to that part of the MCM enterprise that focuses specifically on the processes, policies, and infrastructure required to take a product concept derived from a national requirement through research, early and advanced development, manufacturing, regulatory approval, procurement, and stockpiling. A larger framing of the public health infrastructure needs for national health security is described in the NHSS.

The review highlights the need for the enterprise to incorporate a strategy that balances the ability to quickly produce MCMs for unknown

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threats as well as the current strategy of countering identified threats. This new strategy is articulated through the following vision: ***Our Nation must have the nimble, flexible capacity to produce MCMs rapidly in the face of any attack or threat, known or unknown, including a novel, previously unrecognized, naturally occurring emerging infectious disease.***

Findings in several key areas led to the development of the new strategy, including: (1) enhancing regulatory innovation, science, and capacity; (2) improving domestic manufacturing capacity; (3) providing core advanced development and manufacturing services to development partners; (4) creating novel ways for the enterprise to work with partners; (5) developing financial incentives, (6) addressing roadblocks from concept development to advanced development; and (7) improving management and administration within the enterprise.

The review recommends new infrastructure initiatives as well as enhancements to the current system. The new initiatives include: (1) enabling innovative regulatory science and oversight, (2) fostering flexible manufacturing and advanced development core services partnerships that focus on new platforms for novel product development and manufacturing, (3) expanding the product pipeline by exploiting new concepts emerging from the science base and addressing multiuse potential for these products, and (4) consideration of the development of an independent strategic investment firm for innovation in MCMs. The enhancements to the existing enterprise include: (1) strategic leadership, program, and administrative changes; (2) updating the requirements for current and future products; and (3) a multi-year budget planning process. Transformation of the enterprise is thus comprised of all of these initiatives and enhancements taken together.

The goal of these recommendations is to achieve the forward-looking "sustainable medical countermeasure enterprise sufficient to counter health incidents…" called for in the NHSS. The federal agencies involved in this review, including the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC) and the Departments of Defense, Homeland Security and Veterans Affairs, understand the need for improving existing processes for the betterment of the entire MCM enterprise and are committed to the transformative changes necessary to make this happen.

Medical Countermeasures Review

"I called for this comprehensive review because in order to get the 21st-century countermeasures we need to keep us safe, 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… 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. In other words, we want to create a system that can respond to any threat at any time."

– Health and Human Services Secretary
Kathleen Sebelius, December 1, 2009

I. BACKGROUND

The federal government began work over a decade ago, during the Clinton administration, to develop and stockpile medical countermeasures (MCMs) against biological threats. Events after September 11, 2001 led to an acceleration of those efforts. Major programs to develop and purchase new products for the national stockpile were launched, enabled by a dedicated budget to prepare the Nation against selected threats. These efforts produced a new smallpox vaccine, enabled acquisition of antibiotics for treatment of, and prophylaxis against, anthrax infection, and added other products needed for defense against threats like botulinum toxin.

The passage of the 2004 Project BioShield Act and the 2006 Pandemic and All Hazards Preparedness Act set the conditions for a much wider role by the federal government in managing the development of MCMs for the Nation. The U.S. Department of Health and Human Services (HHS) became the lead for federal public health and medical response to public health emergencies and incidents. Project BioShield provided the HHS Secretary greater authority and flexibility to facilitate the research and development of medical countermeasures and established a Special Reserve Fund to procure these medical products up through the year 2013. It also provided the FDA with specified mechanisms to permit the emergency use of drugs, devices, and biologics that have not yet been approved, as well as use of approved products for off-label indications, upon a declaration by the HHS Secretary of an emergency that justifies emergency use of a product based on a determination of an emergency by the Secretary of Defense, Homeland Security, or HHS. Building on prior efforts, in 2005 the Nation developed a strategy for preventing and responding to pandemic influenza and an accompanying implementation plan. In 2005, Congress passed the Public Readiness and Emergency Preparedness Act, which provided immunity from tort liability to those who make, distribute, and administer MCMs that are specified in a declaration issued by the HHS Secretary. Overall, investments made in support of pandemic planning further stimulated the ca-

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pacity for making and distributing MCMs for this dangerous, naturally occurring, highly infectious disease and enabled a robust response to the 2009 H1N1 influenza pandemic with vaccines, antiviral drugs, diagnostics and devices.

Even with these new authorities, funds and capabilities, there are still significant challenges in MCM development. Project BioShield provides funds to procure MCMs once they are reasonably far along in the development pipeline and provides the most visible assurance to industry about the government's intent to provide a market for these products; however, filling the discovery and developmental pipeline with needed product candidates eligible for Project BioShield against important chemical, biological, radiological, and nuclear (CBRN) agents has been slower and more costly than anticipated, as has been maintaining and sustaining the federal stockpile of MCMs. In addition, while the Nation responded swiftly to the 2009 H1N1 influenza pandemic, making and testing vaccines in record time, the vaccines were not broadly available before the virus had spread widely among the U.S. population. While early detection is not the specific subject of this review, one important lesson learned from the sequence of events during the start of the 2009 H1N1 outbreak in Mexico was that better-resourced surveillance systems in countries throughout the world, and the availability of faster, more robust diagnostic devices, may have led to the detection of the novel influenza strain earlier, providing several additional weeks of planning and perhaps, an earlier start to efforts to make a pandemic vaccine. Earlier detection may have allowed more vaccine to be available earlier, especially given the initial slow virus growth and low yields obtained using current, traditional technologies. Still, even with earlier notice, the response to a newly emerging infectious disease threat would be greatly aided by faster methods to develop and manufacture a vaccine or other countermeasure.

In recognition of these challenges, Secretary Sebelius with the support of the President, called for a review of the "entire medical countermeasures enterprise" in a speech before the American Medical Association's Third National Congress on Health System Readiness in December 2009. The President further signaled his commitment to ensure our Nation is as prepared as possible for these threats in his 2010 State of the Union address, telling the American people that the U.S. Government would be "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."

The National Health Security Strategy (NHSS) of the United States describes ten strategic objectives necessary to achieve a national vision of health security. Among these is the need to promote an effective MCM enterprise "encompassing the full range of competencies, capabilities,

and processes that will provide critically needed vaccines, diagnostics, treatments, and other measures to prevent, identify, and respond to a wide variety of intentionally delivered threats from emerging CBRN sources or from naturally occurring threats from emerging infectious diseases, including pandemic influenza." In its broadest context, the comprehensive capability begins with threat identification, whether through intelligence information or robust public health surveillance, and ends with the timely and appropriate distribution and administration of that medical countermeasure to the threatened and/or affected public, whether it be in a geographically defined area, in the case of a deliberate release, or the entire Nation, in the event of a pandemic.

The MCM enterprise exists to develop, manufacture, procure, stockpile, and eventually distribute products deemed critical to protecting or treating our population against a variety of naturally occurring or intentionally delivered CBRN threats. However, this MCM enterprise does not exist in a vacuum. It is part of a complex, multicomponent system of capabilities necessary to protect our country from a wide range of health threats.

This document was prepared in response to the Secretary's request for a review of the MCM development enterprise. HHS recognizes that there are multiple components and organizations essential to the timely development, deployment, and use of MCMs, including critical investment in the Nation's public health system. Indeed, absent the means to detect a health threat or distribute and administer an MCM, investments in the development and manufacturing of MCMs are of limited value. While recognizing these important dependencies, this review is limited to that part of the MCM enterprise that focuses specifically on the processes, policies, and infrastructure required to take a product concept derived from a national requirement through research, early and advanced development, manufacturing, regulatory approval, procurement, and sustained stockpiling. A larger framing of the public health infrastructure needs for national health security is described in the NHSS.

In reviewing established policy around the MCM enterprise, it is clear that the continually evolving threats of emerging diseases that occur naturally, as well as the increasing availability and capabilities of synthetic biology for good and for evil, necessitate an enterprise with a broader mandate against all of these threats and an imperative to position the Nation to respond to novel and unknown threats. The review identified key ways for the enterprise to shift from the current strategy of developing products aimed at countering known threats to a longer-range anticipatory strategy that balances the need to produce MCMs for known priority threats with the recognition that the Nation needs the flexible infrastructure capacity to rapidly produce an MCM in the face of a new attack or unknown threat. A description of how the review was conducted can be found in **Appendix 1**.

II. VISION

Our Nation must have the nimble, flexible capacity to produce MCMs rapidly in the face of any attack or threat, known or unknown, including a novel, previously unrecognized naturally occurring emerging infectious disease. In support of this vision, this review recommends shifting the current strategy, which has been based largely on the capability to respond to known threats, to one that also anticipates the range of both recognized and novel threats – manmade or naturally occurring – we could face in the future.

III. KEY ATTRIBUTES OF A FORWARD-LOOKING STRATEGY

The key attributes of this forward-looking strategy are as follows.

- The strategy and subsequent MCM investments address clearly defined high-priority current, future, and unknown threats.

- The MCM development strategy embraces nimble, multiuse technology platforms and products, when appropriate, to increase the likelihood of developing and procuring products in a cost-efficient and timely way that constitutes responsible stewardship of resources. The goal is to support multiuse products, platforms, and approaches when possible. Such newer technologies provide product and manufacturing platforms that could, if successful, provide the needed potential to transform our response capacity because of 1) their potential applicability to multiple and diverse threats, known or new; 2) their ability to support more rapid, safer development of a drug, vaccine or diagnostic based on pathogen nucleic acid sequences rather than requiring isolation of an organism, and 3) their potential to support rapid scale up to quantities of product sufficient for large scale emergency use.
- The strategy promotes greater investment in regulatory innovation and enhancement of regulatory science as a lynchpin to success of the MCM enterprise by providing a major return on investment for the public in accelerating the development and approval of a wide range of safe and effective medical products.
- The strategy recognizes that federal government partnerships with innovators in industry and academia are key to achieving success in the area of MCM development. New approaches to collaborations and partnership, and to their financing, are needed.
- The strategy acknowledges that to successfully manage product development, from concept through product use, government scientists from HHS (including its National Institutes of Health [NIH], Food and Drug Administration [FDA], Centers for Disease Control and Prevention [CDC], and Office of the Assistant Secretary for Preparedness and Response [ASPR]/Biomedical Advanced Research and Development Authority [BARDA]), the Department of Defense (DOD), and the Department of Agriculture (USDA) must work with developers, beginning at the early stages of development, to anticipate and resolve problems that could create bottlenecks in the process.
- The strategy recognizes that the federal government must be much more creative in helping inexperienced companies by providing access to core advanced development services, including product and manufacturing, scale-up, pivotal clinical study assistance, and navigating the regulatory process.

IV. KEY FINDINGS

The review identified several barriers to MCM development, as well as significant opportunities for improvement. It recommends that major barriers be addressed through new initiatives to directly enhance product development and use, and highlights that our overall concept for preparedness must shift through time from focusing on developing and stockpiling highly pathogen/threat-specific countermeasures toward a more resilient multiuse platform approach for making countermeasures for anticipated and unanticipated threats. It also found that better internal administration, management, and coordinated integration of the current programs will reduce additional bottlenecks in the MCM development process and better identify and resolve scientific and operational problems when they occur.

The review also identified key opportunities in several areas. These include: enhancing regulatory innovation, science, and capacity; providing core development and manufacturing services to innovators and MCM developers; and expanding flexible, surge-capable manufacturing capacity, including for influenza vaccine production. In addition, the review identified the need for novel ways to work with partners in academia and industry, through public-private partnerships and support for pre-competitive collaborations. Based on the experience with 2009 H1N1 influenza, the review also identified several near-term

needs for government-private sector collaboration to strengthen the developmental and production capabilities of our commercial partners and thus to improve significantly the speed and the volume of vaccine manufacturing and distribution.

Regulatory innovation, science, and capacity

The review repeatedly revealed that aspects of the current regulatory framework and unmet need for regulatory science present both perceived and real barriers for developers seeking to enter the MCM arena. "Regulatory science" encompasses the development and use of new tools, standards and approaches to more efficiently develop products and to facilitate the evaluation of product safety, efficacy, and quality. Advancement of regulatory science and support for a robust scientific capacity at FDA are needed to enhance both the development and the regulatory review of MCM candidates, including products suitable for vulnerable populations (e.g., children, pregnant women, and people with chronic health conditions). There was nearly uniform agreement that strengthening capacity and investment in regulatory science and review, and revisiting aspects of the current regulatory and policy framework, would enable new development and regulatory strategies. Other benefits include greater clarity and more fruitful interaction with product sponsors, especially in areas such as development of new assays, clarification of the "Animal Efficacy Rule," pediatric use of countermeasures, and enhancing the ability and capacity to collect data during emergencies. In the eyes of many industry representatives interviewed in the course of this review, improvements in this area were some of the most important incentives the federal government could provide.

Manufacturing capacity

The Nation currently lacks the domestic manufacturing capacity to rapidly produce and package a vaccine for the American public in the face of a pandemic. The 2009 H1N1 influenza virus struck when the country was in the third year of a five-year strategic plan to attain that capacity; a plan that will need to be revisited based on the lessons of the H1N1 experience and the MCM review. This difficulty in producing, filling, and finishing enough vaccine that could be broadly available before the virus had spread widely is an important reminder of the unmet need for this capacity, as well as of the technical challenges related to virus growth and the ability to produce adequate dose yields and the reliance on old technologies that need to be enhanced or replaced. New approaches to vaccine manufacturing, including the use of recombinant and molecular techniques and the use of new flexible, disposable manufacturing components and multiuse facilities, offer promising ways to meet the demands for efficient, expandable vaccine production capacity while simultaneously meeting needs related to other public health emergency threats.

Providing core advanced development and manufacturing services to development partners

The review consistently found that most of the developers attracted to the MCM arena are small biotechnology companies that bring innovation to the multifaceted process involved in the development of a new product, and in doing so, take on high risk. These companies are often challenged due to limited experience in taking a product through advanced development to licensure. They often lack the capability and/or experience in areas such as animal testing, assay development, product manufacturing, clinical trials, and navigating the regulatory process. For companies that do not have the existing infrastructure to undertake these activities, accessing such services is often too difficult or expensive to assume on their own. This problem is similar to medical product development in other sectors with small downstream markets, such as orphan drugs and drugs for neglected diseases.

Novel ways of working with partners

The review identified the need for public-private partnerships, including nongovernmental entities that can work more nimbly than government could with industry and academia. These public-

private partnerships can assist in the product development process, particularly in areas where the required technologies or science requires rapid adaptation to new opportunities or needs. With regard to vaccine development, some partners with vaccine-specific experience and expertise will be essential to success. The review also found that the federal government can facilitate the achievement of core scientific components of the development process through support for pre-competitive collaborations in which multiple industry partners work together under U.S. Government sponsorship toward addressing a shared challenge. Such partnerships can immediately play a critical role in such important arenas as the development of new methods for influenza vaccine potency assays and sterility assays, and for optimizing virus growth in eggs and cells, all of which have direct impact on annual influenza vaccine production as well as on pandemic preparedness. Similarly, such collaborations can be applied developing new animal models, biomarker or assay development, or new clinical trial analytics/approaches to enhance assessment of a range of products.

Financial incentives

The review process considered the substantial literature on financial incentives for drug development and was informed about the need for increased incentives from many different stakeholders. Some stakeholders in public meetings held for this review suggested that the government should consider specific incentives – e.g., prizes or tax credits. Recognizing the effect prizes can have on innovation, the Office of Management and Budget (OMB) recently promulgated guidelines urging federal agencies to consider broader use of prizes as an incentive to facilitate the "Open Government Initiative."

Reducing roadblocks from concept development to advanced development

The review confirmed the well-known problems of having insufficient numbers of reasonably mature advanced products in the pipeline to be procured under Project BioShield funding. Furthermore, the review found that promising concepts emerging from the research pipeline may not progress to the product candidate stage and into advanced development because their innovators, often academic investigators (e.g., NIH grantees), may fail to recognize that their findings may have important product applications or because investigators lack the wherewithal to proceed to the next stage of concept development. Targeting this early point in the product pipeline may result in a more robust pipeline of products for advanced development. Finally, the review identified a variety of concerns from industry regarding risks they face in product development against these threats, including regulatory risks, liability protection, lack of commercial viability of final products, uncertainty of sustained government commitment, and opportunity costs in developing such products.

Stronger management, administration, and accountability

Dynamic leadership and highly effective governance are essential to the productivity of such a complex undertaking as the MCM enterprise. The review found that while some program management components are working quite well, better management and administration would provide more clarity and predictability, as well as less risk to development partners. These include: improving coordination across the HHS and other departmental agencies involved in the MCM enterprise, a more systematic and consistent approach to decision making, speeding up the contracting process or using more flexible transaction authorities, and improving communication with partners throughout the contracting process. The review also found that the enterprise needs both clearer accountability and more consistent delegation of decision authority across the enterprise, covering both pandemic influenza and CBRN products. Finally, the MCM enterprise as a whole would benefit from clearly setting and prioritizing broad enterprise goals, managing the portfolio of products for a given threat, and coordinating the process of product development itself, from initial concept development to product use.

V. RECOMMENDATIONS FOR OPTIMIZING THE ALL-HAZARDS MEDICAL COUNTERMEASURES ENTERPRISE

The review recommends a series of important initiatives to significantly strengthen our research and advanced development capabilities to provide better incentives to our industry partners, to provide strong leadership, to develop the capabilities and products we need, to integrate the management and transition of programs more effectively across the responsible HHS agencies, to create a more robust and responsive regulatory capacity, and to produce a more dynamic process for continual improvement and assessment.

Taken together, these new initiatives represent a strategy to transform the MCM enterprise.

In coordination with interagency partners and key stakeholders, several recently developed infrastructure initiatives and enhancements were identified that could greatly strengthen the MCM enterprise and, hence, the Nation's public health preparedness. These include: the development of 21st-century regulatory science and greater regulatory assistance to advanced developers; options for providing core advanced development services to commercial and academic MCM developers; infrastructure to expand national capacity for flexible, surge-capable MCM manufacturing capacity, including for influenza vaccine; and additional ways to improve the product pipeline. The review also identified several critical near-term opportunities to improve the speed with which influenza vaccines could be made available and readied for distribution. In addition, the review recommends several administrative and management enhancements to the enterprise. The Administration has identified the resources to undertake the activities described below.

A. New Infrastructure Initiatives

1. 21st-Century Regulatory Science

Enabling innovative regulatory oversight by the FDA is an essential step in transforming the MCM enterprise. The FDA is critical to the success of the enterprise, as it oversees, from a regulatory standpoint, the entire evaluation process of MCMs, including emergency use authorizations (EUAs) and post-marketing surveillance for safety and appropriate use. Enhancement and ultimate application of updated regulatory science and scientific review capacity will help strengthen the MCM regulatory process and thus streamline the MCM development process. The expected outcomes include: (1) guidance on clear development pathways for sponsors can be developed and articulated based on the best possible science; (2) scientific gaps can be identified and, wherever possible, resolved as early and efficiently as possible during the development process; and (3) FDA review capacity can support intensive involvement and coordination throughout the product development process. Three elements described below comprise the proposed 21st-century approaches to regulating MCMs: (1) advancing regulatory science, (2) optimizing the regulatory review process, and (3) optimizing the legislative and policy framework.

Applied regulatory research performed at the FDA and collaboratively with other U.S. Government partners and non-government organizations is needed for the MCM enterprise to better incorporate advances in life sciences research and knowledge into the regulatory process, and to support the development of innovative approaches to meeting public health needs. The FDA needs a stronger, expert scientific workforce and infrastructure if it is to support the intense and highly interactive science-based review that such innovation will require. Supporting the development of these concepts would enhance FDA's capacity to provide guidance on clear development pathways and to identify and solve problems early.

FDA will undertake a new initiative in fiscal year 2011 entitled "Advancing Regulatory Science for Public Health" designed to focus on augmenting the tools used to assess the safety, efficacy, and quality of medical products, with a particular

focus on MCMs, and to get them from concept through the approval process efficiently. Under this initiative, FDA seeks to rebuild its own critically needed scientific infrastructure and capacity to meet the demands of the 21st century and to enhance its scientific collaborations. This initiative will support the identification and qualification of animal models and surrogate measures of product efficacy; expand capability to pre-qualify mobile or convertible manufacturing facilities; improve potency, sterility, and stability assays; all leading to a smoother, faster regulatory pathway.

To accelerate the process from "microscope to market" and enhance regulatory review, the FDA will create new focused Action Teams to work in concert with other components of an enterprise program management team on high-priority MCM products or platforms. The teams, composed of experts from across the FDA, will work with sponsors to identify and help resolve scientific issues as early and efficiently as possible, and to facilitate the more rapid evaluation of these high priority candidates. For each MCM project, FDA and U.S. Government partners (e.g., HHS/BARDA) will work with sponsors to develop a "Regulatory Science Plan" to specify known scientific gaps or opportunities for improvement, and identify priority areas and the required strategies and resources to appropriately address them as needed, before or after project initiation. Demonstrated success of these teams could lead to broader adoption by the FDA for routine use throughout the regulatory process, helping to accelerate the translation of new discoveries and opportunities into real-world products for those who need them.

Finally, the FDA will launch a collaborative project with other HHS and interdepartmental members of the MCM enterprise to better ensure that laws and regulations support preparedness and response. This FDA-led team will work together to optimize the legal and policy framework for MCM oversight and approval. For example, the team will examine mechanisms for potential new or modified approaches such as "restricted or conditional licenses" for products that may be placed in the stockpile and used in emergencies but not marketed otherwise. Furthermore, the team will identify ways to collect product-related data during emergencies that can potentially help support eventual FDA approval and/or post-marketing surveillance requirements. If data gathered by clinical trials sponsored by the U.S. Government support addition of a biodefense indication to an already approved product, the FDA will work with the U.S. Government partners to identify challenges and/or limitations to ensuring that the proposed new biodefense indication is appropriately labeled, including information that may be important for pediatric use. FDA and U.S. Government partners will examine the current constraints posed by the Animal Efficacy Rule and identify strategies to improve its implementation. The team will also make recommendations for any statutory changes that might be required to achieve the goal of improving emergency preparedness and response.

2. Flexible Manufacturing and Advanced Development Core Services Partnerships

Before innovative MCM products and technologies can enter into routine clinical studies, considerable developmental effort is required to overcome the inherent technical, regulatory, manufacturing, and commercial risks. Unfortunately, based on past experience, sole reliance on the original innovator to also take on the roles of developer, manufacturer, and regulatory strategist does not always augur well for eventual success. The general trend is that these development risks are primarily borne by start-up entrepreneurial, or less experienced commercial partners, many of whom would benefit from a much greater "helping hand" in acquiring technical expertise and advice in the steps to move from small to large production and approval of an MCM product. Provision of expertise and infrastructure to address advanced development and scale-up manufacturing would significantly lower barriers to moving innovative products from the labora-

tory to the patient or population needing them. This approach should encompass not only CBRN threats, but novel methods to produce vaccines and other MCMs against emerging infectious diseases, including pandemic influenza.

Assisting our less experienced commercial partners is therefore critical to the country's self-interest in procuring critically needed MCMs. It is also crucial that the United States has access to flexible means to respond to uncertain threats. This review recommends that HHS, either alone or in collaboration with DOD, establishes Centers for Innovation in Advanced Development and Manufacturing that will provide advanced development and manufacturing capability for MCMs to address national security and to augment public health needs on a cost-effective, reliable, and sustainable basis. These Centers will provide assistance to industry and government by advancing state-of-the-art, disposable, modular manufacturing process technologies. They will link our industrial partners with needed expertise and would foster collaborative research to advance relevant science, including interaction with FDA's regulatory science efforts described above. These Centers will furthermore work to improve the application of modular manufacturing and any other emerging technologies to support MCM development.

The Centers for Innovation in Advanced Development and Manufacturing will support the country's advanced development activities for CBRN-related products, and HHS, with U.S. Government partners, including BARDA, will provide guidance and management oversight in terms of specific product objectives. Different capabilities, and perhaps different centers, will be needed to span the known and future technological diversity for making biologics, vaccines, drugs, and diagnostic devices. Finally, in public health emergencies, these Centers may augment existing United States manufacturing surge capacity against emerging infectious diseases or unknown threats, including pandemic influenza.

The envisioned result is an integrated, domestic infrastructure based on strategic partnerships with industry and/or academia with unprecedented flexible and modular capabilities to develop and manufacture new biological MCMs in a timely manner to protect the U.S. civilian population. The Centers will help to support and develop the next generation of the MCM development workforce through training opportunities, including graduate training programs, for current and future industry and government scientists who engage in advanced development and manufacturing of MCMs. The Centers will also be used to explore emerging and innovative technologies that could be applied to current or future MCM development efforts to reduce risk, increase yield, and ultimately to reduce total life-cycle costs through flexible manufacturing, consolidating other costly product development expenditures, or any other economy-of-scale opportunities potentially created by these Centers.

Initial Planned Objectives of the Centers are to:

(1) Provide surge vaccine production capacity for a response to any serious emerging disease threat for which a vaccine is available, including pandemic influenza;

(2) Provide advanced development and production of priority, selected CBRN MCMs;

(3) Provide additional capacity to manufacture clinical investigational lots of candidate vaccines, as well as manufacturing capacity to respond rapidly to emerging infectious disease outbreaks, including those involving previously unidentified microbes;

(4) Provide vaccine production capacity at pilot and/or commercial scale to augment the existing manufacturing infrastructure (e.g., small-market vaccines utilized by DOD, such as for adenovirus vaccine)

Since these Centers are proposed to serve the dual needs of the U.S. Government and our business partners in creating a more robust and efficient MCM enterprise, enterprise partners across government should work with experts from in-

dustry to craft Centers that provide the types of services of greatest deemed significance to the enterprise prior to solicitation of such Centers.

3. Expanding the Product Pipeline and Addressing Multiuse Potential

For the MCM enterprise to succeed and be transformative, it is critical to foster innovation, especially for technologies or approaches that can provide advantages in speed of response, broadened product application, cost containment, and efficacy. Currently, market and financial forces do not provide sufficient impetus for research and development aimed at novel technology approaches for prevention and treatment of emerging infectious disease or CBRN threats. Furthermore, government funding is finite, with many competing expenditure needs. In many cases, potential innovation of the sort described languishes in academic laboratories or small biotech companies. It is often difficult for these entities to successfully find funding and/or partners to facilitate the necessary bridging studies that would carry a potential candidate from an "interesting discovery" to a candidate product firmly established in a commercial pipeline. A major reason for this gap is the inherent risk involved – most individual scientific discoveries do not lead directly to an identifiable product; therefore, the commercial development path and ultimate market are not sufficiently clear to stimulate private investment. Often, this risk calculus can be altered through modest and focused investments supporting pivotal work or through a well-suited partner that has interest and expertise with the particular technology and the ability to make an appropriate risk decision.

a. Exploiting Discovery and Translation of Product Concepts

The U.S. Government cannot overlook the importance of maintaining a strong, vibrant basic research and discovery program to enhance our goals of translating important scientific discoveries into tools and techniques to ultimately be moved into advanced development for eventual licensure and use in a public health or medical setting. This initiative will leverage existing intramural and extramural research programs as well as applied and translational resources throughout NIH, CDC, FDA, and DOD. The government itself has robust research programs and an expert talent pool that is contributing to highly cost-effective intramural programs for discovery and translation of potential MCMs. The NIH supports a large extramural basic research program which would benefit from an increased emphasis and focus on translation of discoveries towards novel technologies, platforms, and products. The DOD, through the Transformational Medical Technologies (TMT) and the Defense Advanced Research Projects Agency (DARPA) also substantially expand the U.S. Government's capacity for engaging innovative academic and commercial experts. In addition, the government's intramural institutional resources can at times provide more rapid, expert, and low-cost development than can our extramural programs, with a higher likelihood of success. Thus, investments in intramural capacities to fuel product-specific development and novel threat research needs should be continued.

Over the last decade, the U.S. Government has substantially increased its efforts to support translation of promising basic scientific discoveries into drugs, vaccines, and devices, including diagnostics that can enhance patient care. The NIH Common Fund, for example, has established a series of cross-cutting, trans-NIH research programs to support interdisciplinary efforts in nanomedicine, bioinformatics, structural biology, and other fields. Through its National Center for Research Resources (NCRR), NIH has established a new program of Clinical and Translational Science Awards (CTSA) to promote cross-disciplinary research and clinical investigation.

NIH has also increased its commitment to providing translational research core services by expanding its Rapid Access to Interventional Development (RAID) program and establishing a National Chemical Genomic Center (NCGC),

a Molecular Libraries Program (MLP), and other initiatives. In the realm of biodefense, the NIH National Institute of Allergy and Infectious Diseases (NIAID) has been a leader in establishing a network of contractors who can provide a complete set of preclinical services to early stage investigators with promising products. Most recently, in the Patient Protection and Affordable Care Act, Congress authorized the creation at NIH of a Cures Acceleration Network to "*conduct and support revolutionary advances in basic research, translating scientific discoveries from bench to bedside*."

CDC has also been at the forefront of translational work for investigation and control of new and emerging infectious agents, such as the development of a veterinary West Nile Virus vaccine and the deployment of a five-target assay to detect subtypes of influenza, including avian strains and the 2009 H1N1 pandemic strain.

Taken together, these elements provide an essential infrastructure for fostering the kind of translational success that is needed. The enterprise must actively identify promising scientific discoveries and consciously expedite their transformation into practical, usable products. We need to ensure that the discoveries NIH supports through its investments in basic science – discoveries that can provide new ways of addressing known threats and that are our only hope against the threats we cannot predict – do not die on the vine, but rather are cultivated and available to be turned into products whose potential utility we may not yet appreciate.

HHS will implement a number of new strategies to carry out this initiative. A key component of this initiative would be Early Development Teams that would work closely with partner agencies and programs (NIH, CDC, DOD TMTP, ASPR/BARDA, and FDA) and with academic researchers, biotech companies, and large pharmaceutical companies to provide strategic guidance for researchers as well as provide appropriate contacts who can assist in moving promising candidates through the process. Bringing new products forward more rapidly would require both a qualified and dedicated staff that understands the mechanics of drug development and the full range of resources that NIH can mobilize in support of such efforts.

Such staff would have incubation of innovation as their only mission. In collaboration with relevant program managers, they would scour grant portfolios and their resulting publications, (performing an "internal tech watch function"), foster program integration and cross-program collaborations, and provide grantees with promising compounds or novel drug targets as well as guidance concerning next steps and support in gaining access to core translational services within NIH. Where necessary, staff could even play a matchmaking function with other investment organizations, and the Center for Product Innovation and Advanced Development, or biotechnology and pharmaceutical firms. Such an approach represents a new and potentially transformational model of advancing our science investments at NIH, and could enable benefits far beyond the realm of MCMs.

Finally, another critical component of such an initiative would be a focused solicitation program for more targeted research, using flexible transaction tools, such as rolling Broad Agency Announcements, to capitalize on emerging concepts and recognized gaps in downstream development programs. This initiative would also collaborate closely with DOD's equivalent medical countermeasure research programs to draw on the strengths of both and would be used to link with ASPR/BARDA for transition of concepts to candidate products at a point where downstream planning could be anticipated to maximum benefit.

b. Immediate Needs Related to Pandemic Influenza Vaccines

This review also identified immediate needs and opportunities in the area of pandemic vaccine development. It recommends the immediate development of better methods for potency assays and sterility testing, and rapid development of

optimized virus seeds for influenza vaccine production. These efforts would best be undertaken through collaboration between influenza vaccine manufacturers and scientists at FDA, CDC, NIH, and ASPR/BARDA. In this context, additional collaborative opportunities should be fostered to immediately address diagnostic device development.

In addition, regardless of the vaccine production technology chosen, bulk vaccine needs to be packaged and made ready for distribution. Current vaccine manufacturers lack the capacity to rapidly "fill and finish" sufficient quantities of pandemic vaccine for the Nation. HHS should immediately develop a network of existing facilities that are pre-qualified and under contract to fill and finish vaccine for U.S. Government-contracted vaccine manufacturers in a public health emergency. This proposed additional infrastructure for influenza would also provide needed capacity for other MCM products.

Finally, this review recommends that HHS support the development of at least three influenza vaccine candidates whose manufacture does not depend on virus grown in eggs or cells in an effort to both increase capacity and ultimately speed delivery of needed vaccines.

4. An Independent Strategic Investment Firm for Innovation in MCM

To provide necessary support for small innovators and increase the odds of moving innovation into successful development, this review recommends that HHS consider establishing and sponsoring an independent strategic investment firm, and seek any required statutory authority to implement this initiative. Just as In-Q-Tel helped the intelligence community (IC) by promoting technology innovation and linking innovative companies to the needs of the IC, so could an MCM strategic investor build the corps of innovators in the MCM area, linking them with the needs of the MCM enterprise.

The envisioned MCM Strategic Investor (MCMSI) would partner with small "innovator" companies and private investors to generate novel technologies for the required MCMs. Its mission would be the development of novel technologies that have the potential for sustainable commercial applications while at the same time demonstrating applicability in the MCM public health space. The MCMSI would display a higher-risk tolerance than currently exists by the US government for these products and accept a longer time horizon. It would endeavor to take a broad perspective on the biotech and technology sectors to look for candidates that are outside the MCM domain but may provide significant collateral benefit to the MCM enterprise if successful.

The MCMSI would be informed by relevant stakeholders in the enterprise, but it would operate independently and outside the government as a 501(c)(3) corporation or other similar alternative. In addition to its own investments, the MCMSI would leverage private capital, provide expert consultation, and link promising companies with potential partners in the private sector. It would facilitate company reach into federal agencies with supporting resources and would focus on translation of new technologies into potential products. The government and the private sector would receive equal amount of reward for equal amount of risk as the private sector investment receives, with return on investment focused on technology and product rather than financial return.

The MCMSI would be staffed and structured to address our most urgent needs, focusing on three areas of particular priority within its overall portfolio, each of which has clear dual use and marketing potential, meeting both MCM and existing medical/public health needs: (1) novel antimicrobials for multidrug resistant organisms (2) novel mechanisms for disrupting pathogenesis through host pathway targeting, and (3) multiuse platform technologies for diagnostics, vaccines/prophylaxis, and therapeutics.

The first focus would help to address the lack of novel antimicrobial compounds in the pipeline that is a growing problem in the face of multidrug-resistant organisms. This represents an

enormous and expanding global public health concern. The President has committed to work with the European Union to address the threat of drug resistance. At the same time, novel therapeutics for drug-resistant organisms would give us more tools to combat emerging organisms or organisms deliberately engineered to resist current therapies. The second priority area would accelerate novel approaches to countering disease by focusing on host pathways utilized by multiple different agents of disease rather than on specific pathogens. Such approaches hold promise for the potential for broad application and circumvention of problems of pathogen evolution and development of resistance. The third priority area would support efforts to develop flexible platform technologies by stimulating the pool of potential innovators who can bring a concept to the point where product developers would be ready to engage.

HHS would first seek statutory authority to create the MCMSI. Then the MCMSI will select an appropriate individual or entity to build it and a commitment to an appropriately sized annual investment from HHS that would form the basis for beginning and developing such an investment strategy. Either way, it would require a staff with extensive experience in the biotech and pharmaceutical industries and with additional scientific and financial expertise as needed to effectively manage the portfolio.

B. Enhancements to the MCM Enterprise

1. Strategic Leadership, Program, and Administrative Changes

This review found that the enterprise would be strengthened by changes in how it is managed and decisions are made.

- MCM Development Leader

  HHS should identify a dynamic leader whose sole job is to coordinate and integrate the multiple efforts and programs within the Department to assist in successful development of medical products for the enterprise. This senior-level position would work with program leaders and managers across the diverse span of product development activities as well as with commercial partners and other key stakeholders, and would help bridge the Department's efforts with other key government agencies.

- Better Agency Coordination

  The Enterprise Governance Board (EGB) was set up by charter to serve as an HHS policy coordinating council for the CBRN portion of MCM enterprise and EGB policy decisions have usually been made by consensus. No equivalent executive-level council operated prior to the 2009 H1N1 experience for pandemic influenza MCM-related decision making. The Countermeasures Steering Committee serves primarily as a decision making forum for influenza MCM procurement and implementation functions, but most policy decisions are made elsewhere in the Department. More recently, policy-level decisions have been made through other meetings of the senior leadership.

  This review recommends that a new leadership construct be established, the Enterprise Senior Council (ESC) to replace the EGB. This council would include all the Senior Leaders of the enterprise to oversee and serve as the decision forum for MCM development policy and implementation. It would incorporate all threats (CBRN, pandemic influenza, and emerging infectious diseases) and would address the range of cross-cutting activities that comprise the MCM development process.

- Coordination and Collaboration with U.S. Government Partners

  Roles and responsibilities for MCM development are not limited to HHS. HHS must work closely and collaboratively with other partners from the DOD, USDA, the Department of Homeland Security (DHS), and the Department of Veterans Affairs to address overarching national program goals and to set and prioritize MCM enterprise needs.

- Systematic Approach to Decision Making

  The enterprise receives significant levels of funding to develop and/or procure critical MCMs. The expense involved in developing or procuring a single product can range upward from hundreds of millions of dollars, and replacement costs escalate the initial procurement to even higher sums. There are many products that the enterprise seeks to produce or buy across multiple different programs. Across this portfolio, senior management must make trade-offs and decisions, and these decisions must be made based on well-defined parameters such as technical, regulatory, and business risks. The ESC should develop and implement a disciplined, metrics-driven, systematic approach to doing so.

- Contracting and Communication

  This review recommends that to the extent possible HHS – in particular, ASPR/BARDA – improve the speed of its contracting and decision-making processes and, within the limits of what is legally permissible, improve its communication with developers throughout the contracting process. This includes information that the business community has consistently requested regarding the size of the projected market and the potential price that the U.S. Government is willing to consider. It is further recommended that HHS finalize the guidelines for the use of Other Transaction Authorities that can provide more flexible, faster ways of procuring goods and services.

- Management of Product Development

  This review found that major opportunities for enhancing the product pipeline would accrue from better, earlier, and more consistent collaboration between U.S. Government scientists (e.g., from NIH, FDA, CDC, ASPR/BARDA, DOD, USDA) and developers. While the need for this has been identified and discussed, additional needs for such coordination were found in areas such as scientific problem solving and setting product requirements to align with intended public health uses of products and components of the regulatory pathway. Processes that ensure such collaboration, from initial concept development to product use, should be used regularly.

- Reexamine How Liability Protection is Provided

  A frequent theme of industry recommendations for strengthening the enterprise was the need for appropriate liability protection for the development, testing, manufacture, and administration of MCMs that lack other commercial application. HHS, together with other government and private sector partners, should review the Public Readiness and Emergency Preparedness Act and its application over the last several years to determine whether it provides the most appropriate framework for providing such protection.

2. Updating the Requirements for Current and Future Products

Defining and prioritizing the overarching MCM requirements are key to the entire research, development, and procurement process. The process begins with threat and risk assessments to include any relevant intelligence information. These assessments underlie DHS Material Threat Determinations which specify those CBRN agents that present a material threat to the U.S. population sufficient to affect national security. Thereafter, the level of investment needed to develop a medical countermeasure capability to mitigate these threats for the civilian community falls to the Department of Health and Human Services. HHS works with a variety of other Departments to assess impacts and determine mitigation strategies. The review has highlighted a need for a strategic reassessment of the U.S. Government's MCM portfolio to determine what changes in requirements, if any, are needed, especially as the enterprise evolves from a threat-specific to a more flexible and capabilities-based strategy,

and an institutionalized process for regularly updating it. This also suggests a need to revisit with the Department of Homeland Security the process for threat/risk assessments to determine whether there has been any substantial change in the underlying basis for evaluating national security risks from existing or future biological agents of concern. Additionally, obtaining end-user feedback about potential MCM uses is an essential element of such a requirement-setting process, which must also account for the needs of pediatric and special populations, groups often considered only after product development for general population needs are met. The proposed Enterprise Senior Council should develop this process and an appropriate method for obtaining and incorporating end-user feedback.

3. Multiyear Planning Process

The Department, as well as each relevant agency (NIH, CDC, FDA, and ASPR), would benefit from developing a coordinated 5-year plan based on the priorities and goals identified in the recommended national strategy for MCMs and tied to measurable outputs and outcomes to allow the Department to track progress toward stated goals. While the annual Budget and appropriations process would still remain the mechanism for budget development, such planning would enable the transition of MCM products across the component agencies within HHS that span the process of MCM development from maturing research through advanced development, procurement, sustainment or replacement of products in the stockpile. Sustaining the stockpile – especially as products purchased earlier begin to expire – is expensive, and the enterprise hasn't fully accounted for, and hasn't had a sustainable way to ensure, lifecycle costs. Finally, this would allow the Department to forecast, plan for and communicate specific corporate needs within the enterprise to best ensure that our MCM enterprise meets our national security goals.

The Pandemic and All Hazards Preparedness Act recognized and provided language that authorized significant funding of advanced research and development costs, after Project BioShield and the Special Reserve Fund proved to be an insufficient incentive for this research and development to occur. The enterprise needs to determine long-range advanced development needs and how best to support them, based on a five-year projected plan. Similarly, a five-year planning process needs to account fully for lifecycle costs of procuring and maintaining all materials placed into the Strategic National Stockpile. This budget planning should include both CBRN and pandemic influenza-related needs.

The development of this long-term plan should be overseen by the Assistant Secretary for Financial Resources with input from the Enterprise Senior Council.

VI. CONCLUSION

Secretary Sebelius called for a review of the MCM enterprise with intent toward incorporating 21st-century technology along with 21st-century financial, legal, and regulatory frameworks into the system. These are changes that would create incentives for companies to build the products we need to defend against the diverse threats we face from naturally emerging infectious diseases as well as intentional acts of terror with biological, radiological, or chemical materials. This review identified a variety of initiatives and opportunities to accomplish these intended goals.

The MCM enterprise needs to institute significant structural and program changes to develop a more robust, aggressive, forward-looking and transformational approach to providing these products. It requires the science and research community to create and transition more candidate MCMs and flexible platform technologies that are poised for successful adoption by advanced product developers. These changes could offer better capabilities and incentives to effectively support industrial partners. The enterprise must establish unique ways to partner between government and private organization scientists, working together to build next-generation science and advanced development centers for scalable and agile production capabilities. Furthermore, the enterprise must, without delay, stimulate resurgence in scientific and infrastructure investment in our regulatory organizations to strengthen their capabilities for providing the most timely and up-to-date technical advice and review for these products. Synchronizing and effectively managing all of these new initiatives and the program as a whole will require both new and reinvigorated tools that create and sustain a workable, integrated system. Ultimately, none of this is possible without strong leadership, shared vision, balanced and sustained resources, and well-understood objectives across all of the agencies and organizations within HHS to reach the goal of a responsive national capability for the current and future public health emergency threats.

Finally, this review recognizes that fulfilling the goals of a successful MCM enterprise – i.e., the timely provision of appropriate MCMs when needed – ultimately rests on a strong public health system, which requires improved global and national surveillance, a trained workforce, and the infrastructure, including links to the health system, that enables delivery and administration of MCMs at the right time and to the right people. These foundational elements of an effective MCM enterprise are framed by the National Health Security Strategy and the Department's specific plans to advance the readiness of the public health system will be articulated in the first NHSS Biennial Implementation Plan. Given the important dependencies, the strategies the Department will articulate in the Biennial Plan will be harmonized with and build upon the recommendations made in this MCM review.

Appendix 1

HOW THIS REVIEW WAS CONDUCTED

The review acknowledged that there are multiple threats, as well as numerous risks and scientific, technological, and regulatory challenges, in the development of medical countermeasures (MCMs) – a field where time lines are long and risks of failure are great. Rather than review the enterprise accomplishments or challenges associated with each specific threat, or reprise a massive body of science, the review focused on the systems foundational to the enterprise and highlights the issues inherent in development, manufacture, procurement, and public health uses of medical countermeasures. Many aspects of the program work well, and progress is being made on a daily basis to ensure that the nation has appropriate protections against identified public health threats, but there are additional, comprehensive steps that can be taken to optimize the system for successful outcomes.

This review was conducted in multiple steps. The first step reviewed a large body of work on medical countermeasure development, financial and market incentives, and procurement of science; on the needs of the end-users of MCM products; and on mechanisms to get products to those users. Second, the successes of enterprise efforts to date were examined to identify the critical components for and impediments to success. In addition, numerous opinion leaders were interviewed, including those that have been previously involved with enterprise activities and who were well positioned to comment on successes and lessons learned. Representatives from the pharmaceutical and biotechnology industry and their investors, and leaders in state and local public health were also interviewed. A series of meetings and workshops were conducted during which aspects of the MCM enterprise were discussed and debated, including: a two-day workshop hosted by the Institute of Medicine's (IOM's) Forums on Public Health Preparedness and Drug Development, a forum at the National Association of County and City Health Officials Preparedness Summit, and a meeting of the President's Council of Advisors on Science and Technology.[1] Finally, the ASPR, on behalf of the HHS Secretary, asked the National Biodefense Science Board (NBSB), an HHS Federal Advisory Committee, to convene a workshop to review the overall strategic management, leadership, and accountability structure of the MCM enterprise and write a report synthesizing the issues and challenges with recommendations to improve its effectiveness.[2]

Representatives from across HHS,[3] Federal Interagency partners,[4] and the Executive Office of the President participated in these meetings, reviewed the material, and assisted in challenging and vetting the issues contained in this report. This larger group advised on the process, inputs, and findings of the review, and was called upon to help represent their associated parent organizations' views.

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[1] Proceedings for these workshops can be found at: http://www.phprep.org/2010/Agenda/Schedule.cfm.

[2] Of note is that prior to the decision to undertake this review, the NBSB had reviewed issues related to the sustainability of the market for the MCM enterprise and released a report in February 2010 that serves as a complement to its current recommendations regarding overall strategy, leadership, and management of the MCM enterprise.

[3] ASPR, CDC, NIH, FDA, the Office of the Assistant Secretary for Financial Resources (ASFR), the Office of the Assistant Secretary for Planning and Evaluation (ASPE), the Office of the Assistant Secretary for Legislation (ASL) and the National Vaccine Program Office (NVPO).

[4] The USDA, DOD, DHS, and VA.