

MEETING REPORT

FLEXIBLE DEFENSES ROUNDTABLE MEETING: PROMOTING THE STRATEGIC INNOVATION OF MEDICAL COUNTERMEASURES

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ON MAY 10, 2007, THE CENTER for Biosecurity of the University of Pittsburgh Medical Center convened an invitational meeting to discuss a national strategy for developing “flexible defenses” against chemical, biological, radiological, and nuclear (CBRN) threats. This was the second of two meetings held by the Center to discuss issues related to those aspects of the Pandemic and All-Hazards Preparedness Act (P.L. 109-417, passed in December 2006) that are intended to improve the development of medical countermeasures for national security threats.¹

The Act requires that the Department of Health and Human Services (HHS) deliver to Congress on June 19, 2007, a strategic plan for developing medical countermeasures against CBRN threats. The first Center for Biosecurity meeting, held on March 22, 2007, discussed administrative and implementation issues of Title IV of the Act, including the role of the Biomedical Advanced Research and Development Authority (BARDA), how medical countermeasure procurement processes might be improved, and the essential elements for successful leadership of BARDA.² In the May meeting, participants focused on the January 2007 Homeland Security Presidential Directive 18 (HSPD-18), which requires HHS to develop a *flexible defense strategy*—defined as “a rapidly deployable and flexible capability to address both existing and evolving[CBRN] threats”—using the Title IV authorities in the Pandemic and All-Hazards Preparedness Act.³

The concept of a flexible defense is still a term of art. There is limited consensus on what it could or should mean. Meeting attendees and interviewees (“participants”) expressed a range of views on the possible goals of a flexible

defense strategy for medical countermeasures and how those goals might be implemented. These diverse views, summarized in this report, will need to be evaluated for their technical feasibility and prioritized, as the nature and proportion of countermeasure investments in a national flexible defense strategy are refined.

Meeting attendees (listed in the sidebar) included present and former U.S. government officials, members of the biopharma industry and venture capital community, and academic experts. The daylong discussion addressed the rationale, goals, feasibility, and implementation of a flexible defense. In advance of the meeting, the staff of the Center for Biosecurity interviewed 35 people, including representatives from the biopharma industry, such as the Alliance for Biosecurity;⁴ present and former government officials from HHS, the Department of Defense (DoD), and the National Institutes of Health (NIH); and academic researchers. The purpose of the interviews was to elicit their conceptions of what a national flexible defense strategy should entail and how it might be implemented. The results of the interviews were distilled and presented to meeting attendees to inform the discussion. Individual comments made during the meeting were not for attribution, and there was no effort to reach consensus within the group.

RATIONALE FOR PURSUING A FLEXIBLE DEFENSE STRATEGY

The costs and logistical and technical challenges of developing and stockpiling medical countermeasures against each

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CBRN threat are considerable and possibly prohibitive. The costs of developing and licensing a single drug or vaccine have been estimated at \$880 million to \$1 billion,⁴ and 8 to 10 years typically are required to reach licensure.^{5,6} Acquiring sufficient quantities of medical countermeasures for the Strategic National Stockpile and maintaining these supplies adds further expense. The 2006 Bioterrorism Risk Assessment, carried out by the Department of Homeland Security (DHS), included 28 biological agents that could lead to deliberate exposure of civilian populations.⁷ Genetically engineered threats, to be considered in future DHS risk assessments, will further expand the number of agents. In addition, new biothreats will continue to emerge from naturally occurring diseases, as SARS did in 2003. The large number of potentially destabilizing biothreat agents, and the high costs of developing and procuring medicines and vaccines against the entire range of CBRN threats and emerging infectious diseases such as pandemic flu, spurred interest in possible alternatives to a “one bug, one drug” strategy of stockpiling specific countermeasures against each CBRN threat. Moreover, rapid and important advances in the biosciences and in biotechnology raise the prospect of new and more efficient approaches to drug and vaccine development and production.^{8–10}

The plan to direct some U.S. government countermeasure investments toward the realm of flexible defense is stated in two recent government documents. Homeland Security Presidential Directive 18 (HSPD-18), issued January 31, 2007, cites the impracticality of developing and stockpiling medical countermeasures against every possible threat and states that the U.S. government should pursue novel medical countermeasures that could be used against multiple threats. Specifically, the U.S. government “will target some investments to support the development of broad-spectrum approaches to surveillance, diagnostics, prophylactics, and therapeutics that utilize platform technologies . . . [and that flexible defense] goals could include identification and use of early markers for exposure, greater understanding of host responses to target therapeutics, and development of integrated technologies of host responses for rapid production of new countermeasures.”³

The HHS Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Strategy for Chemical, Biological, Radiological, and Nuclear Threats, published in March 2007, also states that HHS intends to pursue a new CBRN medical countermeasures strategy “to mitigate risk within time and cost restraints.” Specifically, HHS aims to develop and/or acquire “broad-spectrum solutions using technologies that enable more flexible next-generation interventional concepts and to consider approaches and technologies derived from the commercial drug development sector to support the biodefense mission.”¹¹

POSSIBLE GOALS AND STRATEGIES

Meeting attendees and interviewees suggested three possible, and not necessarily mutually exclusive, goals for a flexible defense strategy against CBRN threats. Any or all of these goals could be pursued as complements to HHS’s existing “fixed” countermeasure acquisition strategy, which procures products specific to single biothreat agents. The discussion did not examine the scientific challenges, costs, or time frames involved in meeting the proposed goals.

1. Broad-spectrum products that could be used against a wide range of threats. Broad-spectrum medical countermeasures could be developed and stockpiled prior to an emergency and used against an array of agents when needed. Participants offered a number of examples of broad-spectrum countermeasures that might be pursued, including broad-spectrum antibacterials and antivirals; drugs designed to counter the clinical consequences of infection, such as sepsis or inflammation; products that boost innate immunity; and treatments to minimize the transmission of a contagious disease (e.g., a medical treatment that reduces coughing might limit the spread of a disease and reduce the number of victims, even if it does not benefit the individual patient). Other broad-spectrum products might include point-of-care diagnostics capable of diagnosing asymptomatic infections caused by a variety of agents. The ability to rapidly and accurately identify who is infected (or not) and with what agent could have strategic value by informing decisions about how to distribute limited quantities of medical countermeasures and who should be isolated to prevent spread of disease.

2. Technologies that enable rapid, cost-effective development of drugs and vaccines against a wide range of threats. In addition to flexible medical countermeasure *products*, some meeting participants and interviewees suggested that flexible *technologies* could be developed to accelerate countermeasure development and production, thereby reducing development costs (possibly for a wide range of medicines and vaccines not related to CBRN defense) and enabling rapid development and production of needed countermeasures in response to attacks employing unanticipated threat agents or attacks requiring quantities of countermeasures that would exhaust stockpile supplies. The capacity to very quickly produce large quantities of countermeasures might also diminish the need to maintain large and expensive national stockpiles.

A number of “platform technologies” that might prove to be useful in developing a range of different countermeasures (as well as non-defense-related medicines) were identified. Examples included: RNAi, a potential platform technology that could be used in therapies against a variety of

biological agents, such as ebola, SARS, or influenza; prophylactic and therapeutic antibodies; DNA vaccines; and virus-like particles (VLPs).

It was also suggested that better animal, *in vitro*, and *in silico* models of diseases and toxicity could accelerate the discovery and selection of new countermeasures. Advances in manufacturing technologies and surge capacity might enable rapid production of large quantities of medical countermeasures, such as monoclonal antibodies, during an emergency. Such enabling technology goals would not only have significant implications for medical countermeasure production; they also might improve the overall drug development process. Many of these same technology goals are cited in the FDA Critical Path Initiative as essential for future drug development for routine medical purposes.^{12,13}

Other technologies discussed by participants and interviewees included countermeasure enhancements, such as adjuvants (to boost the effectiveness of smaller amounts of a medical countermeasure); temperature stabilization processes (to ease the distribution and storage of medical countermeasures); and innovative delivery mechanisms (such as oral doses or patches, for ease of use).

3. Integration of existing knowledge and technologies to facilitate the development of countermeasures against a wide range of threats. A number of participants and interviewees said that flexible defense should focus on improving the application and integration of existing technologies. Many felt that, in general, “we don’t use what we already know.” For example, technologies exist to quickly diagnose and characterize some diseases, but rapid, point-of-care clinical diagnostic tests for identified bioterror agents are not available.

If a disease outbreak occurs against which there are no medical countermeasures known to be effective, it would be useful to rapidly screen existing licensed drugs for efficacy against the disease. As licensed drugs already have been evaluated for safety and have established manufacturing protocols, they could more quickly be used against new diseases if they were found to be effective. No process currently exists to organize such a rapid screening effort, but one could be developed.

In the case of diseases against which no licensed drug is effective, existing technologies could be used to rapidly develop new vaccines or therapies and test them for efficacy. In an emergency, approaches should not be ignored just because they are not on the cutting edge of biotechnology. For example, technologies used to make vaccines in the past—growing large quantities of a virus and “fixing” (killing) the virus so it is no longer infective—could be rapidly tested and produced in an emergency, using modern manufacturing techniques. Prophylactic and therapeutic antibodies also could be tested early on for effectiveness against a new disease.

ORGANIZATIONAL ISSUES WITHIN THE U.S. GOVERNMENT

Many of the meeting participants and interviewees noted that U.S. government efforts are not currently optimized for developing a flexible defense. To improve the situation, some suggested that the government could coordinate its efforts across HHS and DoD; adapt its research, procurement, and regulatory mechanisms to meet flexible defense goals; and develop stronger partnerships with the biopharmaceutical industry. In addition, the U.S. government would need to increase its financial investment in flexible defense.

Coordination Across the Government

1. Coordination of flexible defense programmatic initiatives between HHS/NIH and DoD. Collaboration between DoD and HHS/NIH on medical countermeasure development is currently managed through interagency committees, but many meeting participants thought that coordination would have to be significantly enhanced to effectively develop flexible defense countermeasures. There is value in scientific redundancy, but the government could cost-effectively pursue more diverse projects if there were more coordination among agencies. HSPD-18 also emphasizes the importance of coordinating efforts: While the Secretary of Defense should have exclusive responsibility for the development and procurement of countermeasures to protect the Armed Forces, and the Secretary of HHS for civilian populations, “the Secretaries of [HHS] and Defense shall ensure that the efforts of the [DoD] and HHS are coordinated to promote synergy, minimize redundancy, and, to the extent feasible, use common requirements for medical countermeasure development.”³

Initial efforts to pursue flexible defense within HHS/NIH and DoD could be coordinated to avoid duplication. For example, NIH has funded the bulk of countermeasure research, including alternative delivery technologies, and has pursued research on adjuvants for influenza vaccines. Within DoD, the Defense Advanced Research Projects Agency (DARPA) has pursued the Accelerated Manufacture of Pharmaceuticals program, which is intended to create a rapid, cost-effective manufacturing system capable of producing 3 million doses of GMP-quality vaccines or monoclonal antibodies within 12 weeks. The Defense Threat Reduction Agency (DTRA) has initiated the Transformational Medical Technologies Initiative program (TMTI), which focuses on developing broad-spectrum defenses against intracellular bacterial pathogens and hemorrhagic fevers. These (and several other) efforts in DoD and HHS would benefit both military and civilian populations and could be coordinated with HHS countermeasure efforts.

2. *A national “Tech Watch” program for flexible defense should be systematic, deliberate, and linked to funding across the government.* Most meeting participants thought existing HHS and DoD “technology watch” efforts should be more robust and coordinated across agencies. HHS and DoD have programs to scan for new, potentially transformative technologies that could benefit medical countermeasure development, including those aligned with flexible defense goals. Traditional government outreach mechanisms, including Broad Agency Announcements (BAAs) and Requests for Information (RFIs), were thought to be insufficient to capture the relevant technologies being pursued by private industry. Most biopharmaceutical firms do not monitor these announcements. Moreover, some participants noted that the expense of preparing responses is considerable and that HHS’s past failure to respond to or acknowledge companies’ responses was discouraging.

Participants suggested that HHS needs to be more proactive in its efforts to scan and fund new technologies. One program some participants cited as a possible model is the Defense Department’s Defense Venture Capitalist Initiative, which engages venture capitalists to scan small companies for technologies that DoD needs and in which they can invest.¹⁴

Adapting HHS Requirements and Procurement Processes

1. *HHS will need to revise its requirement-setting and procurement processes for flexible defense products.* Disease-specific working groups at HHS set requirements for medical countermeasures, which are then formulated into Requests for Proposals (RFPs), or Broad Agency Announcements (BAA). For example, there are working groups for anthrax and for botulism that evaluate what countermeasures the government needs. Currently, however, there is no working group that considers the products, processes, and technology integration initiatives that would be needed for flexible defense and how those efforts should be prioritized.

2. *Aligning early research with procurement goals at HHS and NIH.* Some participants and interviewees suggested that HHS/NIH pursue a “project team approach,” in which the entire research and development pipeline is coordinated from basic research to manufacturing and procurement. In the private sector, those responsible for late-stage, advanced development of products or technologies typically have a role in early-stage research; there is no bright line between phases of development. Those responsible for late-stage product development may have valuable suggestions about the direction of early-stage research. NIH and HHS already have project teams to coordinate early and advanced development, but many participants felt strongly that this function could be more robust and that new coordination approaches should be tried.

Another suggestion was to institute a DARPA-like model, in which HHS/NIH program managers would be given broad latitude to quickly fund and defund many parallel projects.

3. *Minimizing technological and regulatory challenges for flexible defense products.* Many participants thought that the task of defining an appropriate animal model for a disease eclipsed the difficulties in creating a drug to treat the disease, and that the government should do more to promote animal model development. The FDA Animal Efficacy Rule¹⁵ allows for the approval of medical countermeasures without efficacy testing in humans if a suitable animal model(s) can be found. But for many bioterrorism agents, suitable animal models have not yet been developed. While NIH has invested in animal model research, some participants thought that their data should be more widely shared among industry and academic researchers. Moreover, even if an adequate animal model exists, restricted access to the model and to the pathogen can greatly delay testing. For example, one company has a licensed broad-spectrum antibacterial that has been in the queue for primate testing by USAMRIID for 6 years. There are limited facilities for conducting such tests.

For some in the biopharmaceutical industry, the notion of a flexible defense was appealing specifically because “dual-use” products that had indications for use in diseases that people regularly contract could be tested in humans, obviating the need for testing within the context of the “animal rule.” Such a course would presumably ease FDA regulatory approval for CBRN indications. For example, the two products approved under the Animal Efficacy Rule were not novel CBRN products but had other uses: pyridostigmine bromide, approved in 2003 for use after exposure to Soman, a nerve agent, had previously received FDA approval for treating myasthenia gravis; and hydroxocobalamin, indicated for victims of cyanide terrorism, was approved in France for treating the effects of smoke inhalation.^{16–18}

4. *The U.S. government could invest in “enabling technologies.”* Technologies that aid in the development of products generally are not typically pursued by biopharmaceutical companies. While every company could conceivably benefit from new *in vitro* models of disease or novel drug and vaccine manufacturing technologies, the company that invests the most in developing these technologies benefits *least*, as it bears the costs of development while other firms enjoy the benefits of imitation. Thus, it has been a traditional role of government to invest in enabling technologies that benefit entire industries. In this case, government could invest in animal models, reagents, and other “toolbox” technologies that would allow pharmaceutical companies to more quickly validate their technologies and products and submit them for FDA approval. Many of these needed enabling technologies have already been listed by the FDA Critical Path Initiative.^{12,13}

5. *A clear, more explicit “map” of how new medical countermeasures should be validated and regulated is needed.* Without processes for the government to partner with industry to define the path to approval for biodefense countermeasures, few companies will choose to work on these products. The government could make it easier for companies to test potential compounds and technologies that may be applicable to flexible defense. Some participants thought that at least some biopharmaceutical companies have drugs that, while not commercially viable, could be tested for their potential as effective countermeasures. One possible model for a testing program could be the NCI Developmental Therapeutics Program, which facilitates the discovery and development of medical interventions for cancer and AIDS.¹⁹ Company representatives also requested clarification of whether products that have both a defense and commercial market will be allowed to be sold commercially.

Stronger Partnerships

The government should develop stronger partnerships with the biopharmaceutical industry. Engagement of both smaller biotech companies and large pharmaceutical firms has been identified by both HHS and the Congress as a desirable goal. Some participants believed that large biopharmaceutical firms might be more engaged if “flexible defense” products were defined in a manner that included products with a commercial purpose in addition to biodefense uses.

1. *Streamline contracting for medical countermeasures.* As was the case in the March 2007 meeting, the importance of forging living partnerships between HHS and biopharma companies engaged in biodefense was emphasized. Meeting participants and interviewees urged that HHS communicate what they intend to procure as early as possible and with greater specificity. Participants also urged that awards be made more quickly. These and similar recommendations are discussed at length in the BARDA roundtable meeting report.²

2. *Government could more actively share its bio research intentions and resources with industry.* Some industry representatives are unaware of useful government resources, such as a National Institute of Allergy and Infectious Diseases (NIAID) website (www3.niaid.nih.gov/biodefense/research/resources.htm) that lists screening and training programs. NIH, DoD, and other agencies could actively inform companies about the existence of these resources. Similarly, the biopharmaceutical industry would be interested in federal research interests and investments, including contract research, being more effectively displayed and visible to improve the potential for effective public-private collaborations.

3. *Government should specify the purpose and indications for a particular flexible defense product, but it should leave the*

product mechanism up to the developer. Participants urged HHS to clearly describe product specifications, including the indications for which the countermeasure or technology is desired, how much the government intends to purchase, and the metrics by which the product will be evaluated. These participants thought that the specific development pathways and mechanisms of action of countermeasures should be left to the industry to determine, to encourage innovation and the development of novel intellectual property.

4. *The government could offer financial incentives for participation in flexible defense efforts.* Small biotechnology firms have established biodefense business models, but in general investors see biodefense projects as risky ventures. In large biopharmaceutical companies, biodefense is seen as a “nonprofit” endeavor that must compete with other nonprofit investments (e.g., research and drug development into public health problems such as malaria and TB). The government might stimulate industry participation in flexible defense by providing financial incentives for companies. Some participants suggested that the government could create prizes and regulatory or market rewards (e.g., tradable FDA priority review vouchers, market exclusivity, and patent extensions). The market exclusivity that biopharmaceutical companies receive if they test their drugs for effectiveness among pediatric populations was noted as a successful incentive that might serve as a model for flexible defense countermeasures.

Discussants also urged the government to involve the financial community in discussions of biodefense research and development, and to identify obstacles to attracting capital to biodefense, since shareholders ultimately decide what products biopharmaceutical companies pursue. One suggestion was to lift the restriction on companies that receive more than 49% venture capital funding from participating in the SBIR grant process.*

5. *Increase communication between government and industry.* Many meeting participants and interviewees thought that government officials should make a much greater effort to communicate directly with biopharmaceutical companies to understand what it would take to get their involvement. There were several references to the relative success of the federal effort to develop and procure pandemic flu vaccine. Many participants thought this success was due in part to the clear signal of the government’s commitment, exemplified by the President’s meeting with the

*In 2001, the Small Business Administration changed the rules on how much venture capital funding a small business could receive and still be eligible for SBIR grants. The change, which prohibits businesses receiving more than 49% backing from venture capital firms from being eligible for SBIR grants, was enacted out of fear that large venture capital firms were trying to corrupt the original intent of the SBIR program. However, in the capital-intensive biotech industry, many companies with promising technologies have significant VC funding and are thus locked out of the SBIR program.

CEOs of the top flu vaccine manufacturers,²⁰ which reassured companies that investment in pandemic flu vaccine development would be rewarded.

CONCLUSION

Many meeting participants and interviewees believed that a national medical countermeasure strategy should incorporate all three of the flexible defense goals mentioned: (1) broad-spectrum products; (2) technologies for fast, cost-effective development of drugs and vaccines; and (3) integration of existing products and technologies to facilitate the development of countermeasures against a wide range of threats. In general, participants felt that these flexible defense goals were technologically feasible and economically appropriate and that they could be pursued simultaneously. For the most part, participants did not examine the scientific barriers related to near-term feasibility of these goals during the meeting, and such technical discussions and evaluations will be important for HHS to pursue. In addition to evaluating the technical feasibility of these suggested goals, HHS will need to prioritize the goals for funding and development.

Although participants generally felt that the flexible defense goals discussed were laudable, some cautioned that they would take a long time to attain. Much research (and many research dollars) will be required to realize the goal of an effective antiviral arsenal or an innate immune stimulator, for example, and most of the promising “platform technologies” are in early stages of development. Some participants saw flexible defenses as part of a long-term strategy. But given the long timelines of developing new products and technologies, as well as the expanding range of CBRN threats, some stressed that it would be important to begin investing in flexible defense now. Participants were careful not to dismiss “fixed” defenses entirely, stating that there will always be a role for disease-specific medical countermeasures.

Many thought that flexible defenses could be expected to have benefits beyond security against CBRN threats. Flexible products and technologies may contribute to global public health and could lower healthcare costs by reducing the cost to make pharmaceuticals. And unlike a fixed approach, flexible defense products would likely have broad commercial markets, attracting large biopharmaceutical companies to participate in biodefense.

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