

Biodefense R&D: Anticipating Future Threats, Establishing a Strategic Environment

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THE ULTIMATE OBJECTIVE OF THE U.S. CIVILIAN BIODEFENSE STRATEGY should be to eliminate the possibility of massively lethal bioterrorist attacks. A central pillar of this strategy must be an ambitious and aggressive scientific research, development, and production (R&D&P) program that delivers the diagnostic technologies, medicines, and vaccines needed to counter the range of bioweapons agents that might be used against the nation. A successful biodefense strategy must take account of the rapidly expanding spectrum of bioweapons agents and means of delivery made possible by 21st century advances in bioscientific knowledge and biotechnology. Meeting this challenge will require the engagement of America's extraordinary scientific talent and investments of financial and political capital on a scale far beyond that now committed or contemplated. The purpose of this article is to provide a brief analysis of the current biomedical R&D&P environment and to offer recommendations for the establishment of a national biodefense strategy that could significantly diminish the suffering and loss that would accompany bioterrorist attacks. In the longer term, a robust biodefense R&D&P effort, if coupled to substantial improvements in medical and public health systems, could conceivably render biological weapons ineffective as agents of mass lethality.

THE PROBLEM: 20TH AND 21ST CENTURY BIOWEAPONS

The advantage is now firmly with those who would seek to deploy offensive bioweapons; the state of biodefense is relatively weak. Following the terrorist attacks of 2001, the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) received \$1.7 billion to fund biodefense research projects. NIAID has since established a "roadmap" de-

scribing the scientific research needed to devise new "countermeasures" (i.e., diagnostic technologies, therapeutic drugs, and vaccines) for the pathogens thought to be the bioweapons agents of greatest concern.^{1,2} Much of the NIAID roadmap has, appropriately, focused on developing countermeasures for the six CDC Category A bioweapons threats (anthrax, smallpox, plague, botulism, tularemia, and the viral hemorrhagic fevers) for which there are striking gaps in available countermeasures (see Table 1), and a selection of other bioweapons threats on the CDC's Category B and C lists (collectively termed "20th century bioweapons" in this article).

Growing numbers of people in the scientific community now recognize that looming just ahead is a far more daunting array of potential engineered bioweapon agents (collectively termed "21st century bioweapons" in this article). The life sciences are at the beginning of a revolutionary period. Scientific understanding of living systems and how to manipulate them is expanding exponentially, fueled by advances in computerization, the global dispersion of bioscientific expertise as well as biological databases, and substantial economic investment in biomedical and agricultural research and product development.^{11,12}

A prime example of these powerful advances was the identification in 2001 of the approximately 40,000 genes in the human genome.^{13,14} Scientists are rapidly learning how to translate this genomic "parts list" into a sophisticated understanding of how specific genes control human biological systems in the body. Such discoveries will bring great benefit to humankind, but they will also allow the development of a new constellation of powerful 21st century bioweapons.

There are already countless portents of the coming power of bioscience and how it will propel bioweapons developments. Scientists have shown that it is possible to create strains of the bacterium that causes anthrax to be resistant to the most powerful existing antibiotics.¹⁵⁻¹⁷

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TABLE 1. FDA-APPROVED MEDICAL COUNTERMEASURES FOR CATEGORY A BIOWEAPONS THREATS

<i>Category A Disease</i>	<i>Vaccine^a</i>	<i>Post-Exposure</i>	
		<i>Therapy^a</i>	<i>Rapid Diagnostics^a</i>
Anthrax	Yes	Yes ^b	No
Smallpox	Yes	No	No
Plague	No	Yes ^b	No
Botulism	No	Yes ^c	No
Tularemia	No	Yes ^b	No
VHF ^d	No ^e	No ^e	No

^aOnly FDA-approved vaccines, therapies, and rapid diagnostics are considered.

^bThere are limited numbers of antibiotics specifically FDA-approved for these diseases. The knowledge required to create antibiotic resistant strains is in the open literature.

^cAntitoxins can be effective therapies for botulism, but they must be used early—they can only stop progression of paralysis, not revert it. Antitoxins are in very limited supply.

^dVHF = Viral hemorrhagic fevers.

^eA few members of this large family of viruses do have FDA-approved therapies and vaccines.

References: 1, 3–10.

They have demonstrated the capacity to make viruses that can overcome vaccine-induced immunity.¹⁸ Viruses can be genetically modified to increase their ability to kill infected cells,¹⁹ or to become capable of attacking entirely new target species.²⁰ Viruses and bacteria can be manipulated in ways that make them better able to survive environmental stress and to be disseminated over distances in the air as weapons.²¹ Technologies already exist that could be used to protect pathogens from detection or destruction by the human immune system.²² These are only a small sample of the developments ahead on the bioscience landscape.

The “dual use” aspect of bioscience does not pertain only to specific, isolated technological applications, as is the case in nuclear weapons work. Rather, it is biological *knowledge* itself that is the source of the power that can be applied toward beneficent or malevolent ends. The knowledge needed to engineer a more lethal viral or bacterial bioweapon is essentially the same as that needed to understand how that virus or bacteria causes disease and how to create an effective vaccine against it. The distinction between good biology and its “dark side” lies only in intent and application.¹¹ With rare exception, it will be very difficult to sequester new bioscientific knowledge that might be applied to building biological weapons without simultaneously harming beneficial biomedical research and essential biodefense R&D&P.^{11,23}

Given the size, momentum, and global dissemination of the bioscientific enterprise and the great demand for the medical and agricultural products being created, the

rapid global advance of bioscience is essentially unstoppable. A successful biodefense R&D&P strategy must accept that the growth and international diffusion of bioscientific knowledge and technologies will continue at a phenomenal pace and must seek to leverage these powerful forces against the bioterrorist threat.

VISION OF VICTORY: THE SHAPE OF THINGS THAT MUST COME

The trajectory and pace of bioscience, coupled with terrorist groups’ interest in inflicting catastrophic casualties, demand a biodefense strategy that anticipates attacks using novel, unforeseen bioweapons agents that are more virulent and behave differently than organisms found in nature. Such attacks using novel bioengineered pathogens are plausible even in the near future, and this possibility should be among the core planning assumptions of a U.S. biodefense strategy.

Responding effectively to large-scale attacks using engineered bioweapons would require the identification of the new pathogen and its novel characteristics, the design of effective therapeutic and preventative medicines, and the mass production of these products—and all of this would have to be accomplished rapidly enough to prevent catastrophic loss of life and forestall grave social and economic disruption. The process of moving from “bug to drug” now takes up to ten years.²⁴ The U.S.

biodefense strategy must set as one of its key strategic goals the radical shortening of this process.

The rapid production of such countermeasures in the aftermath of a bioterrorist attack would be to little avail unless the nation also possessed the public health and medical capacity to distribute medicines and vaccines to affected communities with great speed and efficiency and to provide care for large numbers of sick people suddenly needing medical attention. With few exceptions, most communities do not yet have these capacities.^{25–28}

Despite the breadth and magnitude of these challenges, if sufficient strategy, leadership, and resources were brought to bear, the U.S. could leverage its prodigious bioscientific talent into a biodefense R&D&P program capable of producing new countermeasures on an emergent time-scale, and could establish the medical and public health systems necessary to care for great numbers of victims of bioterrorist attacks. Were this all to occur, the strategic advantage would switch to the defense. People could still be killed by bioterrorist attacks, but it would be possible to prevent mass lethality, thereby lessening the attraction of bioweapons as weapons of terror. Biodefense would have the advantage.

The potential consequences of a biodefense initiative of this scale exceed even the lives of victims and the lessening of the threat to social order and democratic processes. A serious biodefense R&D&P program, pursued with investments on a scale appropriate to a major national security threat, would inevitably lead to great veins of knowledge invaluable to reducing the global burden of naturally occurring infectious disease. A recent report by the National Intelligence Council concluded that, in developing countries, “the severe social and economic impact of infectious disease . . . are likely to intensify the struggle for political power to control scarce state resources. This will hamper the development of a civil society and other underpinnings of democracy.”²⁹ Fundamental discoveries in the science of infectious disease, joined by great innovation in drug development and production processes, as well as revitalized medical and public health systems in the U.S. and abroad, could substantially diminish not only the threat of bioweapons but also the global scourge of infectious disease. This, in turn, might abate some of the virulent passions that can lead to terrorism.

BRIEF ANALYSIS OF THE BIODEFENSE R&D&P ENVIRONMENT

The major bioscience communities have distinct and important roles in countermeasure R&D&P

The bioscientific enterprise may be thought of as three related but distinct communities: university and govern-

ment research labs, biotechnology companies, and pharmaceutical and vaccine manufacturers. Although the scientists and functions of these communities may at times overlap or even merge, each of these sectors has a distinct culture and operates in accord with different business models and reward systems. Biodefense policies intended to engage and leverage the talent and capabilities in the U.S. bioscience community must take into account this range of individual and institutional expectations, priorities, and skill sets.

U.S. public and private sector investment in biomedical R&D&P is significant. In 2002, the National Institutes of Health spent approximately \$22 billion on basic biomedical research; other government agencies contributed an additional \$4 billion.^{30,31} The university scientists who are the chief recipients of these grants perform much of the fundamental biomedical research needed to fuel the development of new medical products.

The private sector investment in biomedical R&D&P is also substantial. In 2001, the U.S. biotechnology and pharmaceutical industries invested \$40 billion in research and development.^{32,33} Unlike academic research, which usually focuses on long-term investigations into biological mechanisms, industrial R&D efforts tend to concentrate on shorter-term product development.

Within the private sector, biotechnology companies can generally be characterized as relatively small, entrepreneurial organizations seeking to demonstrate the viability of one or more products. Their survival typically depends on their capacity to rapidly develop a new product to the “proof of concept” phase (i.e., demonstrate preliminary evidence that a certain drug or vaccine may prove effective). Typically, biotechnology companies do not manufacture large quantities of a drug or vaccine, but sell or license their work to a large pharmaceutical company for further development. The U.S. biotechnology workforce has grown 14–17% annually over the past six years and is expected to reach 500,000 by 2012.³⁴

The pharmaceutical industry consists primarily of large multinational corporations. Five of the top ten pharmaceutical firms are headquartered outside the U.S.³⁵ Pharmaceutical firms are expert in managing the complicated, expensive, sometimes decade-long path between a “proof of concept” and the manufacture and marketing of a licensed drug or vaccine.

Fundamental biological research will be propelled by the academic science community

Essentially all drugs and vaccines on the market today are derived from basic science discoveries. New countermeasures will require fundamental research into the mechanisms that control biological processes and the continuing elucidation of systems of microbial pathogen-

esis and of human immune response to infection. A biodefense R&D&P strategy must push forward rapidly across this broad frontier of basic biological research. Of the distinct domains of bioscience, academic scientists are most dedicated to the pursuit of such fundamental discoveries. Persuading this community of scientists to devote their skills and intellects to biodefense-related research will be essential to a successful biodefense R&D&P strategy.

The historical record shows that scientists have performed great public service in the interest of human health and security. But the bioterrorism threat is unfamiliar, and its dimensions are not yet fully comprehended by much of the academic bioscience community. The most talented university scientists will not be attracted to a biodefense research initiative unless the R&D program is structured to take into account the necessary incentives, processes, and challenges of university-based research.

Academic bioscientists are motivated by many different ambitions, but most share the goal of making fundamental contributions to the store of human knowledge. Most hope that their work in some way will eventually lead to improvements in human health. In large part, bioscientists are not yet persuaded that fundamental discoveries or great improvements in human health will be direct objectives (or even corollary benefits) of biodefense research. On the contrary, despite explicit statements by NIH leaders that basic science will be an integral component of biodefense,³⁶ many academic scientists believe that biodefense research will have as its objectives applied research projects aimed at near-term development of a specific product, such as the next generation anthrax vaccine or a rapid diagnostic test for smallpox. Scientists are more likely to engage in biodefense research if they become convinced that highly innovative—"cutting edge"—research into fundamental biological mechanisms will be at the core of the national biodefense R&D&P strategy, in conjunction with the near- and long-term objectives to develop an array of key countermeasures.

The best academic researchers have grant commitments and projects that have multi-year time horizons. Redirecting a laboratory's research emphasis requires considerable lead-time and involves great upheaval in the lives of researchers, lab technicians, and students. Before many academic bioscientists are likely to redirect their research programs toward biodefense, they will need to see evidence that the government is committed to investment in biodefense R&D over the long term.

Recognition and advancement in the academic scientific world is dependent on publication in peer-reviewed literature.³⁷ Scientists use publication as a means to test and verify each other's ideas and experiments, building on previous work or taking investigations in promising

new directions. Publication and peer review are not just cultural traditions within bioscience; they are engines of progress. If a wide swath of biodefense research is classified for national security reasons, and hence becomes unpublishable, or if scientists fear the possibility that years of work may ultimately be classified, many researchers will choose to avoid biodefense work. Highly burdensome security regulations are also likely to discourage participation in biodefense. From a scientist's perspective, other fields of research would allow him or her to make significant contributions to human health, to pursue investigations that he or she chooses, to discuss his or her work freely with colleagues, and to receive peer recognition.

Finally, academic scientists are deeply influenced by the views of other scientists they respect. Younger scientists' career decisions are greatly affected by the judgments of their mentors. A direct appeal from scientific leaders to the wider research community urging active participation in biodefense research could have a powerful impact.

Engagement of biotechnology and pharmaceutical companies will be critical for countermeasure development and production

It is obvious that even the most brilliant basic research discoveries are of no use for biodefense unless they are translated into effective diagnostic technologies, medicines, and vaccines that can be manufactured in sufficient quantities when needed. How best to leverage the assets of different sectors of the bioscience community to address the government's need to procure affordable countermeasures has been under discussion in the Congress even before the events of 2001.

NIH has had considerable success in promoting and funding basic biomedical research, but it has very little experience with the complex process of transforming such knowledge into licensed drugs or vaccines. Anthony Fauci, the director of NIAID, has acknowledged that "the path to product development has not been a part of [NIAID's] research strategy."³⁶ Although some observers question whether the development and production of biodefense countermeasures is compatible with NIH's historical mission of basic biomedical research, NIH leaders have asserted their intentions to attempt such a transformation.³⁶

There is broad agreement, within and outside the government, that the success of the U.S. biodefense R&D&P effort depends to a significant degree on finding ways to engage the forces of the biotechnology and pharmaceutical industries in the development and production of bioweapons countermeasures. The vision of exactly how—or if—government can induce the private sector

elements of bioscience to participate in creating countermeasures for biodefense is murky and much disputed. There is, however, near consensus that existing government contracting mechanisms and incentives are not appropriate or adequate for biodefense R&D&P.^{36,38} The business culture and expectations of the biotech and pharmaceutical sectors are out of sync with the desires and customary contracting and procurement practices of the federal government at several crucial points. Understanding the nature of these disconnects is essential to crafting a workable biodefense program.

The biotechnology culture is a high-risk, fast-paced environment that can potentially yield significant financial rewards. In 2000, the industry raised \$32 billion in capital, but capital investments and new IPOs have decreased dramatically since then, and annual losses have exceeded \$5 billion for several years.^{33,39} This is not a propitious time to expect biotechnology companies to invest in a new, high-risk research agenda, though some small biotechnology companies may be interested in biodefense R&D&P contracts as a means of maintaining their businesses and pursuing products already underway in a capital-starved environment.⁴⁰ Most biotech companies consume capital rapidly: Investments and decisions to pursue or abandon a project must usually be made very quickly. Delaying projects for several months while funding agencies review grant applications—a routine process in university-based research—can have calamitous financial consequences for biotech companies.

The pharmaceutical industry reports that it invests about ten years and \$800 million to bring a new drug or vaccine to market.²⁴ These costs reflect, in part, the large number of failures that must be borne for each successful licensed product produced. Only 23% of all drugs that enter clinical trials ultimately gain approval.⁴¹ Pharmaceutical firms therefore embark on such investments only after careful research into the potential market size and demand that a new product might be expected to evoke. Such market research is, of course, not feasible for biodefense countermeasures. The U.S. government will be the primary, and perhaps only, customer. Countermeasures may be stockpiled but never used, and the scale of demand depends on whether bioattacks occur and the size of the population affected—variables not accessible to market research.

The biotechnology and pharmaceutical sectors share expectations of high profit on successful products. One analysis indicates that operating margins (i.e., profit before tax) for successful biomedical companies in 2001 and 2002 were approximately three times that of the operating margins for traditional defense contractors during those years.⁴² When entering into a new market, biotechnology and pharmaceutical companies anticipate profits that will reflect the 28% annual operating margins re-

ported by biotechnology companies or the 26% reported by pharmaceutical manufacturers in 2002—not the 7–14% operating margins reported by “traditional” defense industries such as General Dynamics, Boeing, and Lockheed.⁴² These discrepancies in profit partly explain why biotechnology and pharmaceutical companies may be reluctant to deeply engage in biodefense R&D&P. Biotechnology and pharmaceutical firm representatives have argued that the traditional defense contractor profit structure does not take into account compensation for the many high-risk biomedical ventures that fail—some only after many years of investment.

The federal government’s responsibilities as business partner and, if necessary, developer of countermeasures

From the government’s perspective, partnerships with the biotechnology and pharmaceutical industries are fraught with uncertainty. The government may contract to fund development of a drug or vaccine against a particular pathogen thought to be a bioweapons threat, but many uncertainties and surprises lie between the initial stages of biomedical research and the licensing of a useful drug. At the outset, there is no way of ensuring that an effective countermeasure can actually be created and produced. Furthermore, threat conditions may shift and alter the government’s need for countermeasures under development and its willingness to pay for such products. The federal government could find itself in the position of having committed resources to purchase large quantities of a yet-to-be-developed countermeasure, even though it has subsequently become clear that the same resources could buy new, more effective countermeasures based on novel discoveries or technologies.

Much of the biotechnology and pharmaceutical industry regard the federal government as a difficult, even unreliable, business partner. There is concern that federal funding for biodefense could disappear before a company manages to produce a countermeasure that the government will buy, or that the investments required to create a product will not be recovered. There is widespread uncertainty about the intellectual property and technology transfer provisions that will govern biodefense countermeasures, and how existing intellectual property laws, such as the Bayh-Dole Act,⁴³ can be updated or reformed.⁴⁴ It is uncertain, for example, who would own and control the intellectual property associated with countermeasures developed under government programs: Is it the discovering researcher, the company that developed the product, or the government? Also unclear is the degree of influence the government would have over licensing of countermeasure intellectual property and the private-sector marketing of biodefense products.

Liability concerns present special problems in the context of drugs and vaccines that cannot ethically be tested for efficacy in human clinical trials. Biodefense countermeasures are likely to be tested only in animal models—until they are deployed for use by potentially large populations during an emergency. Liability protection for the manufacturers of countermeasures was the primary request made by PhRMA (Pharmaceutical Research Manufacturers Association), the pharmaceutical industry trade group, during Congressional hearings on how best to use legislation to engage industry in biodefense R&D&P.⁴⁵

Determining what combination of specific contractual arrangements, liability and IP protections, and profit margins are politically acceptable and sufficient to entice the talents and assets of biotechnology and pharmaceutical companies into biodefense R&D&P work will almost certainly evolve over time and will require considerable experimentation and adjustment. Some elements of a successful accommodation between the nation's need for a robust biodefense R&D&P program and the needs and expectations of the academic and industrial bioscience communities are already evident. The Bioshield legislation, which was introduced by President Bush in the 2003 State of the Union address and which is currently being debated in Congress, is the start of this process.^{46,47} Senators Lieberman and Hatch have introduced a related bill⁴⁸ that proposes to combine Bioshield's market guarantees with more extensive industry tax and patent benefits.^{40,49}

For some specific countermeasures, if private sector sponsors cannot be found, it may be necessary for the U.S. government itself to create and directly manage new systems of drug discovery, development, and production, as has been suggested by the Institute of Medicine and others.⁵⁰ The Department of Defense's (DOD) previous efforts to contract out the development and production of vaccines have, so far, been highly problematic, although the private sector production of smallpox vaccine for civilian use, managed by the Department of Health and Human Services, appears to be quite successful. These experiences no doubt offer significant lessons for the future and deserve careful scrutiny. In any case, the federal government must urgently undertake an analysis of how biodefense countermeasures can best be produced and what roles the bioscience community and the government should play in this vital national security program.

TOWARD A U.S. BIODEFENSE R&D&P STRATEGY: RECOMMENDATIONS FOR ACTION

Signal strong U.S. government commitment to biodefense and articulate a vision of victory

The first step in establishing a successful national biodefense R&D&P program must be clear statements of the

importance of biodefense from the country's top elected officials and other government leaders responsible for national security. Although the Bush Administration and Congress have taken some useful, incremental steps toward improving U.S. response to bioterrorist attacks, no one in the top echelons of government has yet addressed the overall importance and priority of biodefense in the security of the nation or been assigned responsibility for devising or implementing a comprehensive biodefense strategy. Explicit commitments from the President and his cabinet to establish the R&D&P enterprise needed to protect the nation against current and 21st century bio-weapons attacks would certainly help convince the major segments of the bioscience community that federal investments in biodefense R&D&P will be broad and long term. National leaders should clearly delineate the new biodefense programs that are to be established, and the Administration and Congress should establish mechanisms of clear accountability for these new programs.

Build a biodefense partnership between the federal government and the academic bioscience community

Government and scientific leaders should make a direct appeal to the academic research community to engage in biodefense research in the interest of helping to prevent the catastrophe that could follow large bioterrorist attacks and in the interest of advancing the effort to prevent and find treatments for infectious diseases around the world. Not only do academic scientists need to be persuaded that biodefense research will be in pursuit of these worthy goals, but they must also be convinced that fundamental basic science discovery will be a major thrust of biodefense research. NIH leaders have already explicitly stated that basic biomedical research must be a key component of a biodefense R&D&P effort.³⁶ What has been missing is a clear articulation of the scope and intent of the U.S. biodefense program from leaders with the stature to influence national security policy and the authority to commit the nation's resources to such an endeavor.

Security classification of biodefense research should be kept to a minimum to avoid discouraging university-based scientists from participating. Procedures for classification of publications or for imposing other security measures on biodefense research should be vetted through a transparent process that includes representation from the academic bioscience community.

Adapt NIH research processes to a new national security context

NIH has long overseen extraordinary achievements in biomedical knowledge that have been catalyzed by the NIH's traditional peer-review process for assessing and

funding proposed research. But the biodefense R&D&P program now needed creates national security imperatives and time pressures unlike past NIH initiatives. If NIH is to carry the great share of responsibility for biodefense R&D&P, the time horizons for its biodefense grant process must be substantially shortened. The time required to review grant submissions should be reduced from the current 8–12 months⁵¹ to 60 days, and the time from the scoring and approval of NIH-sponsored research to disbursement of funds must also be greatly abbreviated. Academic scientists being asked to dedicate their careers to biodefense, and biotech companies being asked to take business risks in the name of biodefense, should be given evidence that new mechanisms for funding such research are being established on a fast track.

Make increased use of DARPA-like research processes

If the nation's biodefense R&D&P strategy is to take advantage of the full capabilities of the bioscience community, novel funding approaches should also be pursued. Perhaps the most promising alternative research funding model is that of the Defense Advanced Research Projects Agency (DARPA) of the DOD. DARPA has been highly successful in matching mission-driven defense needs to specific research investments. The DARPA research model allows government program managers considerable leeway to invest in researchers or companies with desired technical capabilities or proven track records that offer some chance of fulfilling DOD's stated mission needs—as well as the authority to rapidly cancel projects that do not perform. DARPA has repeatedly produced breakthroughs such as stealth technology, the global positioning system, and Arpanet (the prototype of the Internet) as a result of this innovation-driven approach to government research investments. Recently, the DARPA model of research has been recognized as an important catalyst for science outside of traditional defense realms: A National Academies of Science report on improving NIH recommended that the Director of NIH be given authority over 10% of the NIH budget each year to fund cutting-edge projects using a DARPA-style approach.⁵² Others have also proposed that DARPA-like funding processes would complement traditional NIH peer review.⁵³

The law creating the Department of Homeland Security (DHS) included a provision establishing the Homeland Security Advanced Research Projects Agency (HSARPA).⁵⁴ HSARPA is intended to address all aspects of homeland security R&D, from shipping container inspections, to information security, to biodefense. The final configuration, scope, mission, and funding level of HSARPA have not yet been finalized. Initial signs indicate that, in the near term, the agency will focus more on facilitating late-stage

product development, as opposed to promoting cutting-edge research.⁵⁵ While late-stage efforts are critical to obtaining real-world products, mission-directed fundamental research should not be neglected. If HSARPA is given adequate funding, a mandate to address biodefense problems, and appropriate managerial expertise, it will have the opportunity to play a vital role in the promotion of mission-oriented biodefense research. A vibrant HSARPA, modeled on DARPA, could provide an additional encouragement for biotechnology and pharmaceutical firms to participate in biodefense work.

Infuse more bioscientific expertise into the federal government

For a biodefense program of such import and scope to succeed, the federal government must be a key actor and catalyst, and a government bioscience workforce of sufficient expertise and size will be a critical component of this. But even now the federal government is at risk of losing key senior scientists and medical and public health experts from the agencies with most responsibility for biodefense.⁵⁶ The U.S. government must dedicate great effort to retain a cadre of senior government scientists, medical and public health experts, and program managers and at the same time recruit the next generation of necessary talent.

Mechanisms should be devised to allow scientists, as well as medical and public health professionals, from academia and the private sector to move more easily into short- or long-term government positions. Aggressive and competitive employment packages, simpler and faster hiring procedures, loan forgiveness programs, and a call to public service could all serve as important incentives. Not only are efforts to retain and recruit top talent necessary for building these key government programs, but if people are able to move more freely into and out of government service, they will bring back to academia and the private sector deeper knowledge of the strengths, limits, processes, and goals of government. Such knowledge of government is now limited in many academic communities and private bioscience companies.

Finally, retaining and recruiting more bioscientific talent into government will result in more extensive representation of leading bioscientific, medical, and public health thought in the senior policy-making circles of government. During World War II, individual scientists exercised great influence on government policy and made extraordinary contributions to the national defense. Since the terrorist attacks of 2001, the science community has issued several reports and made efforts to offer its services to the federal government. But both the bioscience community and the federal government are now too big and too complex to enable individual scientists to wield the degree of influence exercised by Vannevar Bush or

Robert Oppenheimer or Alfred Loomis in the 1940s. The bioscience community lacks historical connections to the government agencies most concerned with security matters, and there is no single person, agency, or Congressional committee that has been designated to be the critical point of contact between government and the world of bioscience. The White House Office of Science and Technology Policy (OSTP) is a logical choice for such a role, and the President's Science Advisor, Dr. Jack Marburger, who heads OSTP, has made clear that biodefense and national security are among his important priorities. Nevertheless, for a nation that is home to a great portion of the world's leading bioscientists, as well as medical and public health experts, there is a striking paucity of such expertise among the top policy makers in the government. The federal government should work to change that.

Identify and bridge obvious gaps between government biodefense needs and the bioscience R&D industry

It should be assumed at the outset that establishing an effective biodefense R&D&P program will be the work of a generation and the product of ongoing experiments and revisions. Ways to bridge the obvious disconnects between the government and industry—for example, the disparity between the operating margins of traditional defense contractors and the pharmaceutical industry—should be made the object of intense and continuous study. The issues involved in crafting a viable partnership between the federal government and the bioscience community are complex, unfamiliar, and too important to be accomplished through the traditional legislative process alone. An ongoing high-level process involving government officials and the bioscience community should be established to advise possible ways to address obstacles to producing biodefense countermeasures. Areas of highest priority that will require resolution or accommodation include: the liability implications of producing or employing drugs or vaccines in emergency settings; the intellectual property rights associated with countermeasure development; research funding for the different pivotal steps in the drug development and production process; mechanisms for carrying out necessary Biocontainment Safety Level 3 or 4 (BSL-3 or -4) research on an industrial scale; and funding commitments to purchase countermeasures that are of sufficient scale to attract the leading biotechnology and pharmaceutical companies.

Recognize that we do not have, and must create, systems to rapidly develop new drugs and vaccines

It will not be sufficient to create government biodefense strategy and product acquisition mechanisms that

merely match the incentives and pace of production within the existing biotech and pharmaceutical industries. The U.S. biodefense strategy must assume that the country may sustain large-scale bioterrorist attacks using unanticipated, engineered bioweapons. In such conditions, it would be necessary to design and produce new countermeasures very rapidly—ideally, in a matter of weeks or months. Such a radical shortening of the “bug-to-drug” timeline will not occur unless transformation of the drug development process itself becomes a central focus of U.S. biodefense strategy. Achieving such a transformation will not be easy and will likely require a combination of incremental improvements in traditional manufacturing processes, a streamlining of regulatory procedures, measures to allow rapid resolution of legal concerns, and technological breakthroughs. Calling on the greatest drug development expertise now extant in the private sector and government so as to be able to collect and act on best judgments, prototypes, or even higher-risk new drug development ventures should be an important near-term goal of the Administration and Congress.

Fund biodefense R&D&P commensurate with the national security threat posed by biological weapons

In spite of recent investments, the U.S. government is not yet funding biodefense R&D at a level anywhere approaching R&D for other high-priority national security threats. Funding for biodefense R&D has substantially increased in the past three years. NIH received \$50 million for biodefense R&D in fiscal year (FY) 2001, \$275 million in FY 2002, and \$1.7 billion in FY 2003.³¹ In FY 2003, approximately \$3 billion was appropriated for biodefense R&D across all the federal agencies.³¹

In contrast to the \$3 billion FY 2003 budget for biodefense R&D, the overall DOD R&D budget (excluding biodefense R&D funds) was 20 times as large, approximately \$60 billion.³¹ The Ballistic Missile Defense Organization alone received \$6.8 billion of those FY 2003 DOD R&D funds for development and testing of antimissile systems – more than twice as much as the entire U.S. government spent on biodefense R&D.³¹ The breadth of the challenges posed by the coming bioweapons threat is daunting. There are major gaps in available countermeasures for the Category A agents (Table 1). New engineered biothreats are on the near-term horizon. There has not been a new class of antibiotics developed in ten years. There are few existing effective antivirals. It takes an average of ten years and an average of \$800 million to develop a new drug,²⁴ and such costs do not even include acquisition and stockpiling. (One million 60-day doses of Cipro at the average wholesale price of \$4.67 per pill would cost \$560 mil-

lion, and even the reduced price of 95 cents negotiated by the U.S. government at the height of the 2001 anthrax crisis would cost \$114 million.⁵⁷) Finally, neither academia nor the biotechnology or pharmaceutical companies are yet actively engaged in biodefense. Given such challenges, it is clear that current federal funding for biodefense R&D&P is now grossly inadequate.

CONCLUSION

The full power of the nation's biomedical research, development, and production enterprise is not yet engaged in biodefense, and given the current environment, funding levels, priorities, and lack of clear vision for the biodefense R&D&P program, large numbers of the best biomedical scientists are unlikely to engage. Current biodefense initiatives, when compared to other U.S. government efforts to address top national security threats, suggest that the U.S. government either does not yet understand the grave nature and scope of the bioterrorist threat or is not prepared to commit fully to a robust biodefense research, development, and production effort. This must change if the nation is to counter the coming bioweapons threat and set the course to eliminate bioweapons as weapons of mass lethality.

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