

Taking the Measure of Countermeasures: Leaders' Views on the Nation's Capacity to Develop Biodefense Countermeasures

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THE PURPOSE OF THIS STUDY was to gather and analyze the views of leaders from academia, government, and industry regarding the capacity of the U.S. to develop biodefense countermeasures and to elicit their recommendations on steps that would improve the nation's capacities to succeed in these efforts.

The anthrax attacks of 2001 hinted at the kind of illness and civil disruption a few letters laden with *Bacillus anthracis* spores could cause. The attacks also began to illustrate the grave impact that larger, more sophisticated bioattacks could have on the country. In the years since the attacks, the federal government has spent more than \$14 billion on civilian biodefense, approximately \$5 billion of which has been allocated for research on and development of drugs and vaccines to counter bioterror agents.¹ This year, the BioShield Act (P.L. 108-276) was passed, with one of its major purposes being to provoke the development of the medical countermeasures (i.e., therapeutic drugs, vaccines, and diagnostic tests) necessary to cope with bioattacks that might befall the nation in the future.

As significant as these steps are, a number of biodefense analysts and leaders from academia, government, and the pharmaceutical and biotech industries have concluded publicly and privately that the measures the U.S. government has taken to date, including the passage of the BioShield legislation, will not be enough to entice pharmaceutical industry leaders into this field and will not produce the countermeasures the nation needs for a truly effective biodefense.

Drug development is a complex, multistep process (Figure 1) that can take from 5 to 15 years (an average of 12 years by one estimate²) and can cost several hundred million dollars (one report puts it at \$800 million²). The absence of drugs or vaccines for SARS and West Nile Virus and the lack of the capacity to rapidly manufacture large quantities of vaccine for pandemic influenza strains have been cited as important indicators of the type of system challenges involved in drug and vaccine development. These challenges will have to be addressed to cope with large-scale epidemics, be they deliberately induced with bioweapons or natural events.

METHOD

This study was performed by a team composed of personnel from the Sarnoff Corporation and the Center for Biosecurity of the University of Pittsburgh Medical Center (UPMC), with the assistance of McKinsey & Company. Interviews were conducted with 30 key leaders from industry, academia, and government. The authors jointly analyzed the results of all the interviews. No attempt was made to draw a consensus from the interviewees: Broadly shared views were identified, and representative comments were selected to illustrate these views. The authors of this report do not necessarily endorse the comments or recommendations of the interviewees.

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FIGURE 1. THE DRUG DEVELOPMENT PROCESS

Selection of key thought leaders for interviews

The authors identified key thought leaders with substantial expertise in biomedical research and/or drug or vaccine development from leading academic institutions, the private sector, and government agencies. Each of the experts, who are listed in Figure 2, agreed to participate in a 1-hour private interview, with the understanding that, although the names of the participating experts would be included in the report, all interview results would be anonymous, and thus were reported to the authors by McKinsey without attribution to any specific participant. A small number of those invited to be interviewed declined. Interviewees were not compensated for their participation.

Interview approach

An interview guide was developed to ensure that a similar set of topics was addressed in each of the discussions. Each interview was generally based on the questions shown in Figure 3, but each was tailored in focus and emphasis to match the expertise and interests of the particular expert. In many cases, available time limited the number of topics that could be explored with a particular expert.

FINDINGS

Analysis of the 30 interviews led to the identification of a set of themes that were touched on by multiple interviewees. These themes are described below. Quotes taken from the interviews appear in boldface italic.

The threat posed by bioterrorism and natural epidemics is significant.

There was wide agreement among interviewees that bioattacks and epidemics could have a profoundly serious impact on the nation. Interviewees believed that an attack would instill significant fear in the population,

lead to substantial reduction in interstate (and, potentially, international) commerce, require enormous government spending to contain, and have a severe impact

“Any high school student can create genetically engineered organisms, so I think they will come. Why would anyone use anthrax to attack a civilian population and not make it antibiotic resistant?”

“With a manufactured flu, we’ll never know if it’s terrorism or natural evolution.”

on the U.S. economy. Most felt that a naturally occurring epidemic caused by an emerging pathogen for which we do not currently have countermeasures is a virtual certainty.

There were a range of views regarding what the most probable bioterrorist scenarios of the future might be, with some believing that attacks with well-known existing bioweapons like anthrax are most likely and others being most worried about attacks with bioengineered pathogens.

“By far the biggest impact will be economic—potentially trillions of dollars if a transmissible agent is used.”

“If Miami were wiped out in a nuclear incident, the people in California would go to church and pray for them. If 1,000 people in Miami died of a transmissible agent and one case showed up in Kansas, nobody in California would go to church; they wouldn’t leave their homes.”

Significant shortfalls in bioterrorism preparedness remain.

Most interviewees agreed that there has been improvement in U.S. biopreparedness since the anthrax attacks of 2001. But they also noted that serious shortfalls remain in the nation’s ability to detect and respond to an attack.

FIGURE 2. EXPERTS WHO WERE INTERVIEWED FOR THIS STUDY

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- Leslie Z. Benet**—Professor, Biopharmaceutical Sciences & Pharmaceutical Chemistry, University of California—San Francisco
- Donald Burke**—Professor, Johns Hopkins Bloomberg School of Public Health; Director, Center for Immunization Research
- Gail Cassell**—Vice President of Scientific Affairs, Eli Lilly and Company
- Larry Corey**—Head, Program in Infectious Diseases, Fred Hutchinson Cancer Research Center
- Michael Goldblatt**—President, Functional Genetics; former Director, Defense Science Office, DARPA
- Peter Goodfellow**—Senior Vice President, Discovery Research, GlaxoSmithKline
- Trevor Hawkins**—President, Molecular Diagnostics, GE Healthcare Technologies
- Peter Hecht**—CEO, Microbia, Inc.
- Jeffrey D. Hermes**—Director of Microbial Biochemistry, Merck
- Joe Hogan**—President & CEO, GE Healthcare Technologies
- Anna Johnson-Winegar**—Private consultant; former Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense
- Donald Kennedy**—President Emeritus & Professor Emeritus, Stanford University; Editor-in-Chief, *Science*
- Ebbing Lautenbach**—Assistant Professor, Senior Scholar, Center for Clinical Epidemiology & Biostatistics, University of Pennsylvania School of Medicine
- Josh Lederberg**—Raymond & Beverly Sacker Foundation Scholar, Rockefeller University
- Ron Marchesani**—Head of Quality, Shire Biologics
- Malcolm MacCoss**—Vice President, Basic Chemistry, Merck
- Joel McCleary**—Chairman, Pharmathene, Inc.
- John S. Parker**—Senior Vice President, Science Applications International Corp.
- Michael A. Parniak**—Professor of Medicine, Molecular Genetics & Biochemistry, University of Pittsburgh School of Medicine
- Howard Pien**—President & CEO, Chiron Corp.
- J. Leighton Read**—General Partner, Alloy Ventures
- John Russell**—Executive VP & General Counsel, Quintiles
- Philip Russell**—Director, Office of R&D Coordination, Office of Public Health Emergency Preparedness, DHHS
- Jerald Sadoff**—Former head of clinical vaccine research at Merck; currently CEO, Aeras Global TB Vaccine Foundation
- Klaus Schafer**—Acting Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense
- Pratik Shah**—Chief Business Officer, Kalypsys, Inc.
- Marc G. Stanley**—Director, Advanced Technology Program, National Institute of Standards and Technology, U.S. Dept. of Commerce
- Roy Vagelos**—Former CEO & Chairman, Merck
- Janet Woodcock**—Acting Deputy for Operations, Food and Drug Administration
- Tachi Yamada**—Chairman of R&D, GlaxoSmithKline
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FIGURE 3. INTERVIEW QUESTIONS

1. Do you think that it is more probable than not that the U.S., or a U.S. interest, will be the target of a bioterror attack, or subject to a major natural epidemic in the next 5 years?
2. If a major bioterror attack or naturally occurring epidemic were to occur in the near future, how prepared do you think we are, as a country, to identify the biological agent(s) used, develop needed therapeutics or vaccines, and then manufacture the countermeasures and move them into distribution channels effectively?
3. What do you think the impact of an attack with an agent that we have no effective preventive or therapeutic treatment would be, given our current capabilities and capacities?
4. Do you believe we currently have an effective and comprehensive national biodefense countermeasure development strategy that will better prepare the country to address this kind of threat, and what role do you believe that BioShield plays in this strategy?
5. What do you see as the key challenges that an effective national biodefense countermeasure development strategy must address from both scientific/technical and business perspectives?
6. What would you do to address the challenges you cited in the previous question? Of all the problems, which one would be the most high-yield and should be addressed first?
7. Do you agree that the U.S. could significantly accelerate the identification of pathogens used as agents in an attack, as well as the development of therapeutics so that we would have the capability to very rapidly develop and manufacture a therapeutic response to new agents (or existing agents for which we currently don't have effective treatments)?
8. If a major bioterrorism attack occurred, most pharmaceutical and biotech companies would want to help but would be faced with decisions about how many resources they could realistically allocate to responding to the attack without permanently jeopardizing their ability to execute other critical functions. What are your thoughts on how organizations would deal with this issue?

There was no doubt that the U.S. public health system would be key to any response, but many thought that public health remains in need of significant improvement. It was noted that physicians and the primary health care system should play a leading role in detection, but are ill-prepared to do so. Some interviewees felt strongly that great benefit would come from new rapid diagnostic approaches that would enable detection of infectious agents from patient samples. They noted that standard microbiological approaches used by most U.S. hospitals or clinics can take many hours or days to identify the pathogens of greatest concern and, in some cases, may simply fail to diagnose many of these infections. As a result, interviewees said, new diagnostic tests need to be developed. Many interviewees thought that the currently deployed biodetection systems (e.g., BioWatch) will not perform as intended and that high false-positive rates will result in frequent and expensive false alarms and decreased public trust.

Planning and coordination of biodefense countermeasure development is currently inadequate.

Most of the experts concluded that there is no integrated plan to develop drugs and vaccines for biodefense. They felt that current efforts lacked coordination, were

“Someone has to create a master plan and talk Congress into funding it.”

too limited in scope, or focused too much on specific threat organisms. This group felt that the process of developing countermeasures for biodefense cannot be dealt with by a plan that funds only independent research programs focusing on the basic science of pathogenesis, immune response, and other basic biological processes without making a similar-sized investment to improve the drug development process itself. Interviewees concurred that basic research is critical but added that the pharmaceutical industry has found that a coordinated approach to actively “translate” those laboratory discover-

“The most important thing is to look for ways to enhance and improve the synergies between the academic and private sectors and the government.”

“It’s up to the government to sponsor interactions between the different industries and assemble the units like a jigsaw puzzle into a complete entity that can deal with everything and speed up the process.”

ies into the drug discovery and development process is absolutely necessary in order to address the inherent complexities of bringing a new drug to the market.

There was a widely shared sentiment that an “organism-by-organism” approach is not an effective long-term

“In industry you put 20 people on one project, and you work on it until it either succeeds or fails. In academia you don’t do that—you diversify your portfolio, which give you lots of ideas, but it doesn’t give you a product.”

strategy for countermeasure development. The number of potential threat agents (and engineered agents) is much too large to have a “one-bug-one-drug” approach. In the long-term, new paradigms for countering infectious disease will be needed, and the overall drug development process must be shortened.

Many interviewees also felt that the current plethora of government agencies and offices involved in biodefense (e.g., DHHS: NIAID, CDC, FDA; DHS: HSARPA, S&T; DOD: DTRA, USAMRIID, DARPA) makes it difficult for biotech and pharmaceutical firms, which have limited experience with the government as a direct customer, to find the right place to engage. The ability to foster these public-private connections is seen as key to a successful biodefense development effort.

Many experts suggested that the implementation of a robust biodefense countermeasure development plan would be enhanced by a “one-stop shop” that would provide: (a) the environment for the collaborative development of the plan; (b) the rigorous project management necessary to execute the plan; (c) facilitation of government and private-sector partnerships; and (d) the infrastructure for the complex process of creating and stockpiling the critical therapeutics. Some experts felt that this organization needed to be a government office, but others

“People in the military-industrial complex know who to go to in DOD and the Congress. People in biotech still don’t.”

supported the establishment of a quasi-government entity that could effectively mediate between government and private industry and serve as an “honest broker” among all of the participating public and private-sector players.

The private sector must be engaged, and BioShield is not sufficient to accomplish this.

Interviewees characterized BioShield as a procurement mechanism by which the government can finance the stockpiling of therapeutic drugs and vaccines against

“Stockpiling is only one tool in the toolbox. It can’t be the only tool. Flu pandemics could easily be hijacked for use as a biological weapon, and stockpiling would not be any use for that.”

bioterror agents. Interviewees believed that the BioShield legislation represents a significant step for the government and demonstrates the seriousness with which the government is taking the nation’s biodefense. The lack of a well-defined market for bioterrorism countermeasures is often cited to explain the small number of new drugs being developed for this use, and BioShield is an attempt to address this shortfall.³ However, most of the interviewees believed that BioShield is only a necessary first step and

“BioShield has no impact on us as an industry. What? Are they going to help us with purchasing? What would drive me to put a team on antibiotics when my commercial people are saying don’t do it, there is no return on investment in it?”

is not sufficient to fully engage industry or to produce the countermeasures that will ultimately be needed.

One common concern was that BioShield does not address the liability concerns of the companies from which countermeasures are sought. Since many of these biodefense countermeasures cannot be tested for efficacy in humans (because the disease is fatal and not naturally occurring), efficacy testing will likely be done using animal models. (Safety testing would still be done in humans.) Therefore, it is possible that the first time that a countermeasure is used in humans—possibly on thousands or even millions of people—would be during a crisis. This scenario has the potential to expose the developer to a significant level of liability because of side effects or lack of efficacy in humans, and many firms are unwilling to shoulder that liability exposure on their own. Similar liability issues have been addressed in the past by the National Vaccine Injury Compensation Program (P.L. 99-660), which provides an alternative to the traditional tort system for resolving claims of adverse reactions, and the complete indemnification granted for the smallpox vaccine (P.L. 107-296).⁴ Interviewees spoke to the strong need to resolve these liability dilemmas.

“The academic community has done a phenomenal job of opening new doors to therapy through science, but you need a drug company to make drugs.”

Some interviewees were concerned that BioShield is limited to purchasing countermeasures that are already available or are in late-stage development. They felt these restrictions severely limit the ability to invest BioShield dollars in early discovery and research programs that are needed to develop innovative new countermeasures—for example, broad-spectrum therapeutics. Many interviewees felt that this resulted in a disconnect between BioShield-funded industry and NIH-funded academia that would limit the effectiveness of BioShield and the overall biodefense countermeasure R&D enterprise.

On opportunity costs:

“You make a new antibiotic and if it’s really terrific you’ll have peak sales of \$300–500M per year. If you make a drug for cancer that extends life by 4 months, you can charge \$40,000 per dose. The difference is so staggering. . . .”

Interviewees noted that a major obstacle to engaging the private sector, especially large pharmaceutical companies, is the “opportunity cost” that big pharmaceutical companies see in developing products for a market that may never materialize. As one recent report noted, “Because antibiotics work so well and so fast, they produce a weak return on investment for manufacturers.”⁵ Many of the experts believe that the major pharmaceutical houses will invest in biodefense countermeasure development to some extent out of a sense of social responsibility, but there is a point at which their fiduciary responsibility to their investors will prevent them from investing significantly in projects that have no foreseeable profit. Thus, many of the interviewees believed that the government should seriously investigate how to provide additional incentives to pharmaceutical companies to participate in biodefense countermeasure development.

The experts identified a number of options that they thought would encourage the large pharmaceutical companies to get more involved. It was suggested that these government incentives might include direct funding of industrial research or providing a better guarantee than BioShield offers of a specific market size at a predetermined price per dose.* Some interviewees suggested that the government could offer developers increased patent life or market exclusivity, either on biodefense countermeasures themselves or on other products in the companies’ portfolios (akin to the Orphan Drug Act P.L. 97-414, which encourages development of new treatments for very rare diseases through tax incentives and market exclusivity agreements⁶). These incentives have the potential to provide increased revenues for the pharmaceutical companies in exchange for taking the risk of developing a countermeasure for a bioterror agent.

*Other federal programs that provide support for research and development include the Advanced Technology Program, In-q-Tel, the Small Business Technology Transfer Program, and the Small Business Innovation Research Program. Each of these programs offers direct help to industry during the development process. However, the cost and complexity of drug development may require new mechanisms for supporting development work.

The countermeasure development process needs improvement.

The interviews explored two key issues related to the countermeasure development process itself: (a) how to

“The opportunity is to build a better defense against emerging infections of all sorts. There’s a dual-use benefit in making those repairs. . . .”

improve the development of new therapeutics, vaccines, and other biodefense countermeasures now (during “peacetime”), and (b) ways in which the countermeasure development process could be accelerated to facilitate very rapid development of potential new drugs in the face of an attack with a previously unknown biological agent.

In general, respondents felt that there is a significant lack of overall investment in and focus on development of antimicrobial drugs and other countermeasures by all sectors (academia and industry). Most of the large pharmaceutical companies have greatly scaled back their anti-infective programs, and only a few still develop vaccines. Some biotechnology companies have programs in this area, but most venture capital funds (the most common source of early biotech funding) are also less interested in funding research and development in anti-infectives and vaccines because of the lack of a clearly defined and ongoing market.

“Rapid development of new drugs is a key technology that we don’t yet have.”

Most interviewees felt that the bulk of federal biodefense research funding is focusing on basic research (e.g., looking at the fundamental biology of pathogens and the human response to infection) and not on developing the tools to accelerate drug development and clinical testing. Without significant advances in development and testing technologies, drug development will not accelerate, even in the face of dramatic basic science discoveries. Many interviewees felt strongly that a large increase in investment in drug discovery and subsequent development and testing will be required to develop the tools needed to address the threat of bioterrorism and infectious disease and to accelerate the countermeasure development timeline.

Of those who commented, most did not believe that there was a single bottleneck in the process that needed to be overcome, but rather they thought that revolutionary changes in the entire process would be required. Further, they believed that changes could be brought about only with an increase in the overall level of funding for anti-infective development in industry, academia, and government. Finally, they believed that the increased activity resulting from the increased funding would have to be executed according to a clearly defined plan.

With the current state of the art in genomics, combinatorial chemistry, and high-throughput screening, many interviewees felt that we are in a position to discover potential drugs very quickly—if there is a coherent strategy and sufficient investment is made toward these efforts. Others cautioned that although much progress has been made in basic science and enabling technologies (e.g., microbial genomics, high-throughput screening), these advances have not yet yielded large numbers of new drugs, suggesting that there may be significant work remaining before a new and expedited discovery process is realized.

Some interviewees suggested that areas that might represent opportunities for improvement in the drug discovery process are in the field of proteomics (i.e., the study of the complex protein-protein interactions that take place within a cell), which might enable the identification of drugs that disrupt such interactions with increased efficacy. Improvements in proteomics and related experimental tools (e.g., high-throughput protein structure elucidation, computer modeling of protein-drug interactions) could improve more rational drug development processes, such as structure-based drug design. These and other approaches have an enormous potential for faster, more efficient drug development, but they have yielded few drug candidates to date.⁵

Many of the interviewees believed that it will prove difficult to accelerate preclinical development and that the iterative process of testing (in animals or in test tubes) followed by chemical modification of a potential drug to improve efficacy and reduce toxicity cannot be shortened. However, others suggested that new technologies could increase the rate at which promising compounds are identified by enabling researchers to better predict what will make a “good” drug before the expensive and time-consuming process of testing and modification begins.

Some interviewees suggested that the components of preclinical development with the potential to be accelerated are toxicity and pharmacokinetic studies as well as animal safety and efficacy studies. For the toxicity and pharmacokinetic studies, advances in computer modeling may enable the rapid identification of compounds that would fail such tests, thus greatly reducing the time needed to identify viable products. For animal efficacy testing, one stumbling block may be the limited availability of testing facilities. Such testing often requires access to BSL-3 and BSL-4 containment facilities in which the appropriate animal efficacy models (i.e., the ability to cure actual infections in animals or protect against them) can be carried out. A few of the interviewees were concerned that the level of funding at these specialized government research centers (e.g., USAMRIID) is currently insufficient and that these institutions are not being sufficiently leveraged given the severity of the threat from bioterrorism. Making more such facilities available may

“Our standard thinking about drug development may not apply here.”

increase the rate at which viable drug candidates can be identified and characterized.

Several of the interviewees also identified two additional levers that could be used to accelerate the development of new biodefense countermeasures. It was suggested that the nation take advantage of the drugs already on the market and develop libraries of these drugs that could very quickly be screened against a novel pathogen in the midst of an epidemic. Because they are FDA-approved and the production parameters for these drugs have already been determined, if one of them, or a cocktail, is found to be effective, the ability to manufacture and distribute it would be achieved much faster than starting from scratch. The nation could work to aggregate (or otherwise gain access to) the many libraries of potential drugs, in addition to already-licensed drugs, that are constantly being developed in academia and industry. This would enable the biodefense countermeasure development process to benefit from the work being done by all developers, not just individual companies or academic centers working in isolation.

The other major realm of potential opportunity to accelerate drug development identified by a number of the interviewees was clinical trials and the FDA approval process. Some interviewees felt that the FDA should reevaluate its risk-benefit standards for biodefense countermeasures. By increasing the acceptable level of risk for biodefense-specific countermeasures (i.e., those that would be used only in an emergency), the ability to move these drugs and vaccines through the development pipeline during “peacetime” could be considerably increased. (Under BioShield, the Secretary of DHHS now has the authority to issue emergency exemptions to FDA approval for biodefense countermeasures, but only during a crisis.) However, other interviewees felt that this alteration of acceptable risk was not necessary and could be detrimental to public acceptance of biodefense countermeasures.

DISCUSSION

We think that a number of important conclusions can be drawn from these interviews. A group of leaders from government, academia, and the private sector believe that there is a strong threat of a large-scale bioterrorist attack or a serious outbreak of a natural epidemic disease such as pandemic influenza in the near future. They generally think that the current U.S. biodefense countermeasure development strategy and process are not sufficient to meet the challenges posed by these threats and that the

active participation of the biotech and pharmaceutical industries will be necessary to this effort, but no such broad participation has yet occurred. Most interviewees believe that BioShield is a good first step toward engaging the private sector, but there are many other complicated challenges to overcome before such engagement will occur.

Many interviewees called for the development of an explicit overall biodefense countermeasure strategy, and many argued for the creation of a single organization that would have the responsibility for monitoring the execution of this strategy and for facilitating the collaboration of academia, biotech and pharmaceutical firms, and multiple government offices and agencies. Interviewees were divided as to whether this new organization should be housed within the federal government or if it could be more effective by sitting between the public and private sectors, perhaps as a government-chartered corporation (like Fannie Mae) or some other quasi-governmental research and development organization.

Interviewees argued that the lack of liability protection for biodefense countermeasure developers must be remedied. Some interviewees suggested that improvement in computer modeling for prediction of the toxicity and pharmacokinetics of a potential new drug was a key step in drug development that could be accelerated. Most felt that increased funding was required to speed up the process by which countermeasures are developed and that this funding would have to be administered according to an explicit plan that distributed these funds to both basic science research and to more applied projects that would address the technologies of drug development and testing.

These interviewees strongly suggested that there are many potential opportunities for substantial acceleration in the biodefense countermeasure development process that should be explored and that the price, cost, and complexity of developing countermeasures are not immutably defined or intractable. Given the threat of bioterrorism, the complexity of creating the necessary medical countermeasures, and the number of as yet unpursued opportunities to rapidly accelerate their creation, the Administration and Congress would be wise to make the countermeasure development process, in and of itself, a topic of intense analysis and action in the months and years ahead.

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