



# The Food and Drug Administration Confronts Homeland and National Security

## Report on a Workshop of the RAND Center for Domestic and International Health Security

Richard A. Rettig

- RAND RESEARCH AREAS
- CHILDREN AND ADOLESCENTS
- CIVIL JUSTICE
- EDUCATION
- ENERGY AND ENVIRONMENT
- HEALTH AND HEALTH CARE
- INTERNATIONAL AFFAIRS
- U.S. NATIONAL SECURITY
- POPULATION AND AGING
- PUBLIC SAFETY
- SCIENCE AND TECHNOLOGY
- SUBSTANCE ABUSE
- TERRORISM AND HOMELAND SECURITY
- TRANSPORTATION AND INFRASTRUCTURE

On December 19, 2002, the RAND Center for Domestic and International Health Security hosted a workshop on the challenges the U.S. Food and Drug Administration (FDA) faces as a result of the chemical and biological threats of international terrorism to domestic and overseas U.S. targets: people and organizations, civilian and military. Awareness of these threats was dramatically heightened by the September 11, 2001, attacks on the World Trade Center and Pentagon and by the distribution of anthrax through the U.S. postal system in fall 2001. Awareness of chemical and biological threats was reinforced in late 2002 by the then prospect of armed conflict in Iraq and the knowledge that Saddam Hussein had used chemical weapons previously against Iran and on his own people. It was widely, but not universally, believed that Iraq had both chemical and biological warfare weapons and capabilities.

The workshop originated from several sources. From 1997 to 2000, RAND conducted an extensive review of the scientific literature related to the risk factors identified as potential causes of Gulf War illnesses.<sup>1</sup> A related report examined the Interim Rule that FDA adopted in late 1990 at the request of the Department of Defense (DoD), authorizing the Commissioner of Food and Drugs to waive the informed consent requirement governing the use of Investigational New Drugs (INDs) in certain military situations.<sup>2</sup> Recently, RAND examined the interactions between DoD and FDA regarding the acquisition of drugs and biologics for defense against chemical and biological warfare agents,

focusing primarily on how DoD ought to respond to FDA.<sup>3</sup> As a result, RAND commissioned a paper by Gail H. Javitt to address how FDA might respond to increased national and homeland security needs for drugs and vaccines.<sup>4</sup> The Javitt paper provided the point of departure for workshop discussion.

The larger stimulus to the workshop was the limited availability of vaccines to protect both military personnel and civilian populations against such biological agents as anthrax and smallpox. The concern for vaccine availability also raised the issue of the adequacy (or inadequacy) of the industrial base. This industrial base issue has been debated within DoD for some time in terms of the advantages and disadvantages of having a government-owned, contractor-operated (GOCO) vaccine production facility. It has been addressed in other venues as well. Most notably, in 2002, the Council of the Institute of Medicine recommended the creation of a National Vaccine Authority. That same year, the Gilmore Commission recommended creating a GOCO for vaccines.<sup>5,6</sup>

In this context, workshop participants agreed that FDA regulation was an important piece of a much larger picture. Accordingly, workshop discussion focused on how FDA might modify its policies and procedures to make drugs and biologics, and especially vaccines, more readily available. However, a tension ran

This product is part of the RAND Corporation occasional paper series. RAND occasional papers may include an informed perspective on a timely policy issue, a discussion of new research methodologies, essays, a paper presented at a conference, a conference summary, or a summary of work in progress. All RAND occasional papers undergo rigorous peer review to ensure that they meet high standards for research quality and objectivity.

© RAND 2003

<sup>1</sup> These included infectious diseases, pyridostigmine bromide, immunizations, stress, chemical and biological warfare agents, oil well fires, depleted uranium, and pesticides.

<sup>2</sup> Richard A. Rettig, *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense*, Santa Monica, Calif.: RAND Corporation, MR-1018/9-OSD, 1999.

<sup>3</sup> Richard A. Rettig and Jennifer Brower, with Orli Yaniv, *The Acquisition of Drugs and Biologics for Chemical and Biological Warfare Defense: Department of Defense Interactions with the Food and Drug Administration*, Santa Monica, Calif.: RAND Corporation, MR-1659-OSD, 2003.

<sup>4</sup> Gail H. Javitt "Drugs and Vaccines for the Common Defense: Refining FDA Regulation to Promote the Availability of Products to Counter Biological Attacks," *Journal of Contemporary Health Law and Policy*, Vol. 19, No. 1, Winter 2002, pp. 37–116.

<sup>5</sup> Institute of Medicine, "Statement from the IOM Council on Vaccine Development," November 5, 2001.

<sup>6</sup> The Advisory Panel to Assess Domestic Response Capabilities for Terrorism Involving Weapons of Mass Destruction (Gilmore Commission), *Third Annual Report to the President and the Congress*, December 15, 2001.

through the daylong discussion with the focus oscillating from the FDA role to the broader issues and then back again to FDA. This report summarizes the workshop presentations and discussion and reflects that tension in some measure.

The workshop was chaired by Dr. Kenneth I. Shine, Director of the RAND Center for Domestic and International Health Security and former President of the Institute of Medicine, and Richard A. Merrill, Professor of Law at the University of Virginia and former Chief Counsel of FDA. It brought together representatives from DoD, FDA, the pharmaceutical and biotechnology industries, the food and drug bar, and the executive and legislative branches of the federal government, as well as health policy analysts from RAND and elsewhere.<sup>7</sup>

### Proposals for Change

Javitt, in her paper and presentation, addressed two issues: the effect of Food and Drug Administration requirements on military and homeland security drug development efforts against bioterrorism, and the changes that FDA might consider to facilitate the provision of safe and effective drugs and biologics for responding to that threat. She reviewed the traditional role of FDA in evaluating the safety and effectiveness of new drugs and biologics before it approves their introduction into the commercial market—a role authorized by Congress based on its constitutional power to regulate interstate commerce. The rationale for considering potential FDA responses to homeland and national security issues, however, stems from the need to protect military personnel and civilian populations from chemical and biological threats. Is the traditional FDA regulatory regime satisfactory for national or homeland security, which are predicated on the common defense clause of the Constitution? Javitt argued that, in the wake of the September 11 attacks, the anthrax episode, and the potential of encountering chemical and biological agents in a looming war with Iraq, the threats against domestic and international civilian and military targets call for viewing the role and mission of FDA in a new light.

Many drugs and biologics developed mainly for military purposes infrequently traverse the entire FDA evaluation process. They are classified as INDs and may have been evaluated in Phase 1 or Phase 2 clinical trials. But they may seldom progress to Phase 3 randomized clinical trials nor be submitted to FDA as a New Drug Application (NDA), and thus may never receive agency approval. The reasons why such products languish in this semipermanent IND status,

which can also be described as “not yet approved by FDA,” are largely economic: Commercial firms find little financial incentive to develop military-use products, and the costs of development far exceed the DoD funds available for such an undertaking. The reasons for drugs remaining in this status are also based on ethical concerns, since the effectiveness of an antidote to a chemical or biological agent cannot be tested on human subjects.

An important antecedent to the present discussion is found in the Interim Rule adopted by FDA in 1990 that allows DoD use of specified INDs in certain military situations.<sup>8</sup> The rule, adopted only days before the Gulf War conflict, authorized the Commissioner of Food and Drugs to waive the informed consent requirements of IND use. FDA delayed converting the Interim Rule to a final rule and nearly revoked it entirely in 1998. However, that same year the regulation was superseded by an act of Congress, which vested authority to waive informed consent for the military use of INDs in the President of the United States.<sup>9</sup> The President, however, could act only after receiving a request to do so from the Secretary of Defense and after complying, for the drug in question, with procedures by which FDA determined were safe and were the best-available prophylactic or therapy for specific threats, as well as that the risk of inaction was greater than the risk of action.

The basic issue for DoD, however, is relatively unaffected by the specifics of law or regulation: The use of INDs in active military conflict is far more complicated administratively, clinically, and ethically than is the military use of FDA-approved drugs and biologics. The complications involve ease of use, recordkeeping, and acceptance by military personnel, Congress, and the general public. Moreover, military use of both INDs and approved drugs involves additional considerations than is true in the civilian context. Javitt suggested the existence of a “regulatory gray zone,” where drugs in between “unapproved and definitely unsafe” and “completely approved and totally okay” fall. More specifically, the zone includes products “thought potentially to be safe and effective” but that have not yet been fully evaluated by FDA. Javitt dubbed such drugs “orphan INDs.”

FDA, Javitt noted, had responded with flexibility in regard to several regulatory challenges in the 1990s. In the first instance cited, FDA adapted to the scientific, clinical, and political challenges of HIV/AIDS by establishing a therapeutic IND and an accelerated

<sup>8</sup> See Rettig, *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense*, for a detailed analysis of events related to the Interim Rule.

<sup>9</sup> Sec. 731 of the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (Public Law 105-261), October 17, 1998.

<sup>7</sup> The Appendix of this paper includes a list of participants.

approval process. It made these changes by modifying existing authorities, without adding new statutory authorization. The second instance mentioned was Congress's amendment of the Orphan Drug Act,<sup>10</sup> which provided incentives for drug development for underserved patient populations by granting seven years of market exclusivity. These flexible responses to civilian challenges suggest that FDA indeed has the capability to respond to the challenges of military and homeland security.

Javitt made five recommendations for FDA change. She proposed:

- *the creation of a new FDA office "for approving products for military and homeland defense."*
- *the establishment of fast-track approval authority for products used in military and homeland defense.*
- *a new category of product approval that recognized the gray zone between totally unapproved and completely approved drugs:*

This interim category would recognize that there is really a continuum along which we evaluate safety and effectiveness, and, depending on the use of the product, we may choose a different point within that continuum at which we deem the product appropriate for administration to either military personnel or civilians.

Products evaluated within this interim category might include strict limitations on distribution, time-limited approval, and elimination of informed consent.

- *products for chemical and biological defense.* Javitt suggested that they should be considered "orphan products" under the Orphan Drug Act.
- *that consideration be given to imposing time limits on INDs.* If evidence shows that a sponsor has basically abandoned the further development of a product, the IND would be withdrawn at some prespecified time.

In the brief discussion following Javitt's presentation, workshop participants expressed mixed opinions as to whether the needs of military personnel and those of civilian populations were similar or different. Some participants regarded these needs as very different, while others found no clear divide between them. Regarding the orphan drug suggestion, participants said that the exclusivity benefit would go only to the firms that got there first, that this would do little to promote the industrial base for drugs and vaccines, and that the tax credit would cover only one-half of

the costs of clinical trials and would be of no benefit to firms without tax liability. Participants returned to these issues in later discussions.

## Defense Needs

Anna Johnson-Winegar, Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense, presented the perspective of the Department of Defense. She emphasized the importance that DoD attaches to FDA-licensed drugs and vaccines for chemical and biological defense. In addition to the recently licensed pyridostigmine bromide for pretreatment against soman nerve gas, she pointed out that the nation was preparing for another conflict with Iraq with "exactly the same set of licensed products that we had 12 years ago."<sup>11</sup> Johnson-Winegar noted that DoD wants to use FDA-licensed products for several reasons: for credibility with military personnel, for acceptability to the civilian population, and for the benefit of outside review that indicates the department's adherence to FDA regulations. But the department does not want to use, or appear to use, military personnel as guinea pigs in allegedly secret—but, in reality, nonexistent—testing programs, as is often charged.

DoD's desire to use FDA-licensed drugs confronts the department with a need to accelerate the entire process of drug and vaccine development, from the basic and applied research investment needed to understand the pathogens in question through the preclinical, clinical, and regulatory stages leading to licensure. In short, DoD investment and management of vaccine development is essential to obtaining FDA licensure.

Johnson-Winegar addressed the similarities and differences between naturally occurring diseases and those arising from biological warfare agents. Naturally occurring diseases include typhoid, yellow fever, malaria, diphtheria, tetanus, poliovirus, hepatitis A, meningococcus, influenza, measles, mumps, and rubella; biological agents that constitute threats include anthrax, botulism, tularemia, smallpox, and equine encephalitis viruses.

In using vaccines to protect against naturally occurring diseases, the actual risk of the disease is weighed against the actual risk of vaccine adverse effects. Conversely, using vaccines to defend against biological agents, the potential risk of direct exposure is weighed against adverse effects.<sup>12</sup> Vaccines for naturally occurring conditions have long proved effective—the result

---

**. . . DoD investment and management of vaccine development is essential to obtaining FDA licensure.**

---

<sup>10</sup> The Orphan Drug Act (Public Law 97-414, January 4, 1983) was subsequently amended by the Orphan Drug Amendments of 1985 (Public Law 99-91, August 15, 1985) and by the Orphan Drug Amendments of 1988 (Public Law 100-290, April 18, 1988).

---

<sup>11</sup> Anna Johnson-Winegar, workshop transcript, p. 35. (All direct quotes in this paper are taken from a conference transcript, which is in the author's possession. When possible, page numbers are cited.)

<sup>12</sup> The threats of both anthrax and smallpox might stem from either source. The difference lies mainly in the route of administration, whether delivered in an aerosol (in a bioterrorist attack) or occurring through an insect bite or another normal pathway.

of good collaboration among industry, academia, and government laboratories. The relatively minor risks of side effects can be compared with the significant benefits, based on data from clinical trials familiar to FDA. For these vaccines, Johnson-Winegar noted, “We have the ability to work through the equations. . . . We can look at [potential liability, side effects, etc.] with concrete hard data.”

In the case of vaccines for biological warfare agents, however, only the anthrax vaccine was licensed, at least until the old smallpox vaccine was recently relicensed. Concerning the anthrax vaccine license, she noted that

the members of the military who are the recipients of this product as well as the senior decision makers as well as the public in general understand that this is a licensed product, and that brings them some level of comfort, security, understanding.<sup>13</sup>

Still, a number of other products, including botulinum toxoid, the tularemia vaccine, and the equine encephalitis virus vaccines, have been in IND status for many years. Johnson-Winegar acknowledged that some criticism should be directed to DoD, which has lacked motivation to get these products licensed. She heartily endorsed Javitt’s recommendation that INDs be granted on a time-limited basis and that some evidence of progress toward licensure be required to maintain IND status.

One important difference between the threat of biological agents to military personnel and the homeland security threat to civilian populations is the degree to which the former is understood. Protection of military personnel involves not only vaccines but also diagnostics, individual protective equipment, and environmental detectors. Moreover, the military threats have been quantified to the extent that the number of kilograms of a potential agent that can be disseminated under battlefield conditions has been calculated. The domestic threat situation, however, is far more vague, uncertain, and unknown. And the route of administration is a differentiating factor: whether the agent is delivered by aerosol or is transmitted by food, water, or some other means.

In a military combat situation, the medical focus is on prophylaxis and therapeutics—protecting personnel beforehand and treating them after exposure. In the civilian homeland security context, however, medical attention must focus on therapeutics, treating exposed individuals after an attack, which highlights the need for quick diagnostic tools. An issue for military personnel, one with both legal and ethical implications, is whether taking one’s vaccines is mandatory, i.e., a condition of work, or whether it is discretionary.

In the civilian setting, compliance with medical treatment is voluntary.

Returning to the need of DoD having FDA-licensed products, Johnson-Winegar stressed the importance of the FDA animal rule.<sup>14</sup> Because the department cannot test efficacy of defensive vaccines or prophylactic products by exposing human subjects to lethal agents, extrapolation from animal data is especially necessary.<sup>15</sup> The implementation of the animal rule for DoD underlines its need for a continuing discussion with FDA and industry about such issues as the appropriate surrogate markers, the amount of animal data needed, and the size of Phase 1 and Phase 2 safety studies.

Also, because DoD’s personnel are mostly healthy young adults, Johnson-Winegar expressed her hope that products could be approved by a “stepwise approval or licensure process” for this population before completing studies for pediatric, elderly, and immunocompromised patients, a requirement of the normal FDA licensure process.

Finally, Johnson-Winegar noted that having FDA-licensed products has logistical, financial, and record-keeping benefits. Licensed products allow DoD to consider the shelf life of products, financial and regulatory aspects of stockpile replacement, maintenance of licensure, and best use of limited manufacturing capabilities if there is not an annual production run for a particular product. These are substantial benefits when viewed in relation to the scale of military efforts.

The discussion that followed raised a number of issues. Stephen Prior emphasized the dynamic of non-state actors possessing biological agents—harm’s way is now wherever such actors decide to attack. As a consequence, DoD’s response increasingly includes protecting U.S. homeland and involves both the National Guard and civilian contractors. Charles Ludlam suggested that it should be easy to develop vaccines for an anthrax or smallpox attack, but that the offense (rogue states or nonstate terrorists) was well ahead of the defense. Gail Cassell questioned the ease of developing vaccines, noting, for example, that good scientific studies and clinical trials have not produced a gonococcal vaccine. Leighton Read asked whether this failure is a result of the limits of the science, or the absence of demand-pull. William Vodra differentiated between FDA’s role as a regulator and

**. . . Military threats have been quantified. . . . The domestic threat situation, however, is far more vague, uncertain, and unknown.**

<sup>14</sup> U.S. Food and Drug Administration, Final Rule: “New Drug and Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible,” 67 Federal Register 37988, May 31, 2002.

<sup>15</sup> DoD ended the testing of biological agents on humans on November 25, 1969, and chemical agents on humans on July 28, 1975.

<sup>13</sup> Anna Johnson-Winegar, workshop transcript, p. 38.

its role as a source of biological research targets. The latter depends on industry, other government agencies, or charitable foundations investing in the research. He also challenged Ludlam's proposition that it should be easy to develop vaccines based on the 15 months of bureaucratic wrangling required to move smallpox vaccine from Centers for Disease Control and Prevention (CDC) refrigerators to DoD. Michael Friedman emphasized the need to focus on what FDA might do in light of Javitt's suggestions. He also argued that industry experience in developing anti-infective vaccines and drugs is perhaps more successful than in other areas of medicine, such as oncology, psychotropic drugs, or cardiovascular disease.

John Smith commented on Javitt's suggested category of less-than-full-FDA-approval. Any mechanism other than full FDA approval confronts a potential problem with negligence claims in court, should problems arise with a vaccine in the case of homeland security. Erika King added that incentives to private industry involvement in developing countermeasures depend less on FDA considerations and more on issues of liability, insurance coverage, and a guaranteed market.

Kenneth Shine spoke on the differences in risk and threat assessment between civilian populations and military personnel. For the former, the risk of adverse effects from a vaccine looms large, but the perception of risk of a terrorist attack depends partly on where one lives. Tampa, Florida, for example, does not represent the same kind of target that Chicago, Los Angeles, New York, or Washington, D.C., does. Military threats, however, require judgment about a particular theater of action (e.g., Iraq) and are quite different. Shine asked how and in what way FDA regulation of manufacturing affected the incentives of private industry to develop vaccines rapidly. Vodra commented on FDA regulation of manufacturing and storage, which he characterized as quite separate from its front-end evaluation of the safety and efficacy of products. He argued, "You have to find some mechanism whereby the system will allow us to respond in less than two or three years to develop a new manufacturing site, once we have got the vaccine identified."

## The Food and Drug Administration Responds

Andrea Meyerhoff, Director of the FDA Office of Counter-Terrorism in the Office of the Commissioner, presented a general overview of the agency's efforts in counterterrorism, including its public health and law enforcement responsibilities. The latter involves investigating and responding to tampered food, blood, radiation-emitting instruments, drugs, vaccines, and

medical devices. She emphasized the public health aspect, especially the agency's responsibility for making safe and effective drugs, vaccines, and medical devices available as countermeasures.

Before September 11, 2001, FDA's counterterrorism effort was concerned mainly with the adequate supply of drugs, vaccines, and other biologics and focused on the two centers dealing with drugs and biologics (Center for Drug Evaluation and Research [CDER] and Center for Biologics Evaluation and Research [CBER]). After September 11, the effort was expanded to the full range of FDA-regulated products (drugs, vaccines, and medical devices) and to the entire agency. The counterterrorism funds available before September 11 totaled \$8.2 million; after the attacks, the funds available rose to more than \$159 million.

Meyerhoff indicated that FDA is responsible in its counterterrorism efforts for both civilian and military populations. Civilian populations generally have lower risks but include groups that may need special attention—e.g., children, the elderly, the immunosuppressed, pregnant women. Also, a public health emergency response to terrorism is more likely to follow a sentinel event, such as a patient contracting anthrax. Conversely, military personnel are generally healthy adults, and their protection is more likely to involve advance preparation.

How do counterterrorism queries come into FDA? They may come from any product developer—industry, another government agency—or from private citizens. Firms in FDA-regulated industries typically have established relations with the agency. Small companies, new developers, and academics without such relations may come through the Office of the Commissioner. These queries are coordinated within FDA by a counterterrorism steering committee that directs them to the appropriate product center within the agency. FDA does not just respond, however, but moreover actively seeks to identify products in development, sources of funding, regulatory questions for which research answers are needed, manufacturing issues needing resolution, and potential manufacturers.

Next, Meyerhoff addressed five FDA regulatory mechanisms that can be used to facilitate the availability of medical countermeasures:

- *The pre-IND meeting.* This occurs early in product development before a request for initial human testing is received; the meeting serves as a way to establish early dialogue between product developers and FDA.
- *The IND regulation.* This requires developers to obtain informed consent from human subjects, secure an Institution Review Board (IRB) exami-

**Combat does not often allow the establishment of clinics, allocation of medical personnel, and education of troops, which are normal requirements of IND use. Protocols for battlefield use of IND products would be very helpful.**

nation of a clinical trial protocol, and collect outcomes data (on either safety or efficacy, or both). To respond to a public health or national security emergency, FDA has developed the streamlined IND, or contingency protocol; these applications are on file for products not yet fully approved by FDA, with indications about how such products are to be used in an emergency. Meyerhoff, commenting on Javitt's gray zone proposal, recognized the desire to increase the availability of certain products but cautioned that an agency concerned with safety could not easily abdicate responsibility for declaring products safe and effective. She also said that time-limited INDs were an interesting idea but that they might risk losing important archival data.

- *The animal efficacy rule.* This rule, officially promulgated in May 2002, pertains to drugs and biologics but not medical devices. It applies when the disease in question (e.g., a biological agent) cannot be introduced ethically to a patient population to test diagnostic, prophylactic, or therapeutic responses. The rule requires that a "scientifically valid animal model" be used but does not stipulate a set number of species. Primates are the best models, but product-by-product review is necessary. The rule also requires Phase 4 data collection, i.e., postapproval monitoring of outcomes.
- *The NDA Subpart H accelerated approval regulation.* This regulation requires the use of a surrogate end point that, according to Meyerhoff, is "reasonably likely to afford a benefit in mortality or serious morbidity." It shrinks the study population required to demonstrate benefit compared to the requirement of a clinical end point. The CD 4 count is an example of a surrogate end point widely used for HIV/AIDS drugs. Immunoglobulin levels may be used in vaccine development. Cipro, for postexposure treatment of anthrax, was approved on the basis of existing accelerated approval authority.
- *NDA priority/expressed review.* This authority allows an application to be submitted in pieces and then be reviewed as it is submitted. This is requested by the applicant at time of submission and is generally used for products of public health significance. This priority review shortens the process from the usual ten to twelve months to five to six months.

Meyerhoff concluded by indicating that FDA seeks to strike a balance between making products available quickly for counterterrorism purposes and ensuring that they meet appropriate standards for safety and effectiveness.

William Vodra commented that Meyerhoff's presentation demonstrated that FDA was more adaptive than most agencies when confronted with the challenges of terrorism. Its primary tool, he argued, was the incentive of making "the regulatory atmosphere more flexible and more responsive." He identified the challenges of getting FDA to speak with one voice; getting the government to speak with one voice by harmonizing the views of FDA, CDC, and the Department of Homeland Security (DHS); and determining whether the current legal structure is sufficiently flexible to accommodate a military crisis. Vodra had been proposing for some time, he said,

the need for a carefully drafted authorization by Congress that the Secretary could invoke to permit the Commissioner [of Food and Drugs] to essentially waive any existing statutory rule and substitute something else in its place. [This would be] an authorization to basically approve a product with the understanding that it did not meet otherwise existing requirements.

Such a statutory authorization would allow rapid response to an emergency, based on the best available data at the time.

Ellen Embry, Office of the Assistant Secretary of Defense for Health Affairs, commented that a hand-in-glove relationship between DoD and FDA had begun to work in connection with the anthrax and smallpox vaccines. She noted that IND use in emergencies communicates the wrong public message and that a new descriptive category is needed. Off-label use of drugs approved for one purpose is presumably safe for other purposes, but effectiveness of such use cannot be assumed. Such drugs are investigational but are no longer experimental. She suggested the need for a category that lists licensed drugs that are approved for one purpose, are presumably safe, and are potentially useful for other purposes.

Embry also stressed the importance of FDA's independence in assuring the public of safety and effectiveness of licensed drugs. She emphasized, however, the need to understand and reduce barriers to IND use when such products are used in military combat and homeland security situations. Such a mechanism requires an understanding of the combat environment and its requirements as distinct from the civilian personal health environment. Combat does not often allow the establishment of clinics, allocation of medical personnel, and education of troops, which are normal requirements of IND use. Protocols for battlefield use of IND products would be very helpful. Meyerhoff responded that it is useful for FDA to hear about the "concrete issues of implementing an IND in the field."

## The Morning Discussion

Following the initial three presentations, participants focused their discussion on the animal rule. Gail Cassell, representing the counterterrorism committee of the Pharmaceutical and Research Manufacturers of America (PhRMA), expressed that she was comfortable with the animal rule for vaccines and antibiotics but nervous about its use for immune modulators. A single valid animal model was risky, in her judgment, because genetic backgrounds were important in determining the effects of immune modulators. “So,” she asked, “shouldn’t we be requiring multiple genetic models or these things being checked in multiple animals with multiple genetic backgrounds, different species?” Moreover, big changes are often observed in going from rats to mice, from mice to humans, in immune modulators. Finally, in addition to safety and efficacy, the long-term consequences of using modulators were another source of debate. Cassell asked what FDA was doing in this regard. She argued that more than a case-by-case review is needed because a valid animal model is a total unknown for immune responses. She then asked about the criteria to establish that a given animal model was valid and when such criteria might be available to drug developers.

Dianne Murphy, Director of the Office of Counter-Terrorism and Pediatric Drug Development in FDA’s CDER, responded to the question posed. When a product works well in two animal models but not in another, she said,

It is how well can you explain why there are differences, and it has to do with that criteria about understanding the pathophysiology. That is why the immune modulators are so hard, because you know this is still not that well defined. And this is where we are actually going to be driven by how much the science can move forward in explaining why humans and monkeys behave the same way. And if you give a drug whose effects are known and you have a difference in the animal response from what you would see if you give it to people, can you explain the different responses to the drug or vaccine? It really comes down to being able to explain the responses, and that is the fundamental way I would look at it.

Michael Friedman interjected that the term “safe and effective” was more a hindrance than help in moving forward. It was time, he argued, for FDA “to actually set quantitative parameters” for defining safety and efficacy. For example, he said,

for a disease that causes a 20- or 30- or 40-percent mortality rate, we will, as an agency, accept an unanticipated serious life-threatening side effect of 0.5 percent or 1 percent or 20 percent. Set it for whatever you want it to be with confidence intervals.

That immediately dictates the size of the safety population you study will be, and this is just real simple mechanics. But it will require a national consensus.

Meyerhoff responded by noting the large number of variables with which one would contend. Friedman characterized that route as leading to “cul de sacs,” or dead ends. Although all factors deserved attention, he urged the agency to state, in effect, that “this product will be approved for otherwise healthy people” in a specified age range:

We are in the habit as a nation, and sometimes I suggest FDA as an agency, of making the perfect the enemy of the good. It is time for the good to move forward. All these other areas are very important . . . but I wouldn’t wait to craft something that is so perfect that it will take five years to design.

The agency’s responsibility, he argued, is to set standards for product approval, not to worry about industry response.

Stephen Prior shifted discussion to how FDA might become less reactive and more proactive. For example, on the issue of “how do we deal with INDs,” which was widely acknowledged to be a problem, he asked,

How do we move from active to inactive and abandoned INDs while protecting that incredibly valuable data that exists in all three categories? . . . Why aren’t we able to create a forum in which that discussion can take place and in which the public can participate and understand why the positions are being put forward as they are put forward? I plead on the basis of what Gail [Javitt] has done, if we can just do that, that it will be a phenomenal advance.

Javitt returned to the IND use question, arguing that use in combat is not for research but for prophylaxis or therapy. Making INDs available in such situations as if they were objects of research, both erodes the research protection and fails to legitimate justifiable therapeutic use. Jeffrey Francer suggested that IND use in homeland security emergencies would have similar problems as those of the military situations. CDC would be asked, he said, to use INDs with signed voluntary informed consent, adverse reporting, IRB review and approval, notations of protocol deviation, and the like. He suggested that Congress give attention to a third category of approval for emergency use or interim approval in situations in which something has to be done. Charles Ludlam suggested that the Department of Health and Human Services think through some gruesome scenarios to inform policymakers about high-risk situations. Leighton Read suggested that the discussion, noteworthy in itself, confronted a conservative FDA

---

**“We are in the habit as a nation, and sometimes I suggest FDA as an agency, of making the perfect the enemy of the good. It is time for the good to move forward. . . . I wouldn’t wait to craft something that is so perfect that it will take five years to design.”**  
**—Michael Friedman**

in any event; somehow a new pathway needs to be considered. Michael Greenberg asked whether the bioterrorism funds had provided FDA sufficient funding, a question that evoked laughter from participants. He also inquired as to whether counterterrorism had changed FDA priorities.

### The Industry Perspective

Michael Friedman, representing PhRMA as its Chief Medical Officer for Biomedical Preparedness, reiterated his earlier view that the workshop provided an opportunity to focus on FDA as a critical component of biodefense. He brought the additional perspective of having served previously as principal Deputy Administrator of FDA. A robust biodefense establishment, he noted, has so many facets that discussion can typically float all over the place. In that context, FDA is critical to but not responsible for all activity. He urged the workshop to focus narrowly on “what we can do to help FDA do what it is charged with doing.”<sup>16</sup>

He suggested two goals for FDA in the area of biodefense. First, FDA should “be the critical component for making sure that there are adequate supplies of fully approved products with enough clinical information to allow for reasonably effective use.”<sup>17</sup> Second, the agency should “set up an environment that reduces the cost and time for development, from preclinical to full approval . . . setting the environment, defining the parameters.”

Given any list of threat agents, current treatment options are “relatively unsatisfactory.” In terms of having evidence-based information about how to respond, Friedman said,

We really are in a horrible situation. . . . My question is: What are FDA’s abilities to influence this, and how can we help FDA mount an appropriate effort to convert more of these [potential response capabilities] to three pluses [+++] and four pluses [++++] rather than [continue] the gaps in situations that exist today?<sup>18</sup>

He argued that FDA could influence two time horizons: an acute horizon for the next year and one that is two to five years out. However, FDA is the arbiter of evidence-based information, not the generator of it—that is someone else’s responsibility.

Friedman focused on specific regulatory concerns. Surrogate markers and end points are appropriate issues. He applauded the animal rule but said “what is really necessary right now is the level of transparency, of consistency, or clarity about how the rule will be uti-

lized, what the expectations are, disease by disease, situation by situation.”<sup>19</sup> On the issue of INDs versus NDAs, he took a polar position: “It is really unacceptable to have [or use] INDs as a way of protecting either the civilian or the military population.” That means getting the necessary resources, expertise, and putting pressure on industry to avoid having to rely on INDs, “because they are a nightmare.” He also expressed great concern about the agency’s inadequate resources.

Commenting on Javitt’s five recommendations, Friedman said the following:

- A new office would solve very little and is undesirable.
- Fast-tracking has its pros and cons.
- A new product approval category is not desirable. The IND is inadequate, but “it is perfectly acceptable to say that an NDA is based on the amount of information that you have at the time” and that a reasonable path to follow is to ameliorate toxicities that appear later.
- Orphan drug status involves incentives to industry, on which he deferred to others.
- Imposing time limits on INDs would not necessarily be an effective “stick” with which to exert discipline.

On the whole, though, Friedman was highly complimentary to the effort by Javitt to generate concrete suggestions. His hope was that concrete expectations would be generated for FDA, and then decisions about needed resources and science or mechanisms could follow.

Kenneth Shine asked what FDA might do in a circumstance in which the need for a specific vaccine became clear. Friedman said that the agency could set clear criteria for approval and standards regarding needed data. FDA could also indicate the areas where data were adequate, citing, for example, “information about primates for fluoroquinolones.”

Dianne Murphy responded as a panelist.<sup>20</sup> She stated that FDA is active on “adequate supply” issues, working with CDC to identify and fill gaps. She said the agency is also active in collaborating with the Department of Energy in seeking safety and efficacy for radiation exposure therapies. Incentives are critical, and the identification of a guaranteed purchaser is as essential as having a manufacturer. She drew on her experience of 1990–1993 with antivirals for HIV/AIDS. Getting therapies for serious and life-threatening diseases may involve surrogate markers, regulated distribution, and use restricted to special populations.

<sup>16</sup> Michael Friedman, workshop transcript, p. 121.

<sup>17</sup> Michael Friedman, workshop transcript, p. 119.

<sup>18</sup> His pluses comment refers to approved drugs and vaccines. Friedman, workshop transcript, p. 122.

<sup>19</sup> Michael Friedman, workshop transcript, p. 125.

<sup>20</sup> Dianne Murphy, workshop transcript, pp. 132–140.

There are “tools in place,” she said, suggesting that new tools may not be needed. She noted that ciprofloxacin was approved using the surrogate marker provision of Subpart H (accelerated approval).

Efforts to develop the exact recommendations for the animal rule, Murphy continued, are complicated as one moves from one area to another, from microbiology to nerve agents or radiation exposure. She asked if it was appropriate, for example, to approve gentamicin for pneumonic plague on the basis that it has been approved for pneumonia. In the final analysis, it is necessary for FDA to declare if a product does or does not work. But tools in place will allow rapid forward movement, especially for special populations and uses. In the event of a massive catastrophe, Murphy said, it will not be the science that drives a decision but the politics or policy.

Murphy indicated that INDs and the stockpile were being addressed with CDC, and the battlefield situation with DoD. “Our goal is to get as many things off IND as we can, to do it by identifying the gaps in the sciences and by indicating how you get those gaps filled.” She argued that there will always be products in the IND stage, and it is necessary to find ways to make them available. She discussed the streamlined IND, for which one could use the patient label and need not use the investigator’s brochure, in obtaining informed consent. But, she said, it is essential to have clear guidance and regulations about adverse effects and about constraints on use. Development of such guidance about use is a major effort of FDA/CDER.

Leighton Read commented on the need for a biodefense industry, arguing that no convincing reason exists to invest in biodefense “because the customer hasn’t been identified.”<sup>21</sup> The government, or its proxy, has not yet stepped up to the issue. A customer, to be effective, has to articulate what is wanted and do so over a sustained period. The latter is especially important for the long lead-time research and development needed for biological countermeasures. Drawing on discussions related to global health, Read proposed *pull* mechanisms—“anything that increases profitability”—that include guaranteed purchase, preservation of intellectual property, and tiered pricing for poor countries. *Push* mechanisms would lower the cost of development by reducing the regulatory burden and increasing outsourced research and development from the National Institutes of Health (NIH). Wall Street investors, he argued, would respond most strongly to pull mechanisms. He illustrated his argument about the interaction of push and pull mechanisms, citing the development of FluMist, which was

just then being approved by FDA as a nasal vaccine for influenza.

Regarding FDA, Read emphasized the importance of not adding to the agency’s current responsibilities, even if it were provided additional resources. He also indicated the need for clarity about the regulatory standards for clinical trials. He contrasted software development, which involves no technical risk but substantial market risk, with drug development, which involves mainly technical, or clinical, risk (i.e., Will a product work or not?). Clarity in reducing clinical risk is extremely important. In addition, FDA regulation of facilities and manufacturing needs more than clarity; it requires a new paradigm involving “a really high-quality dialogue between sponsors and the agency on how to get risk and benefit right.”<sup>22</sup> Changes in FDA “cookbook” regulation of manufacturing strongly affected the FluMist development and illustrate the need for science-based regulation of manufacturing.

Friedman responded to Read with a fundamental question:

Do we want to have FDA with its current broad set of responsibilities and limited resources do what they are doing now, or do we want to change its focus and either drop things off the list or add resources to increase its responsibilities?<sup>23</sup>

He emphasized the need for additional resources (people and money) to allow FDA to respond to changing national priorities. Read suggested that the regulatory function for bioterrorism be done elsewhere, a suggestion Friedman rejected.

Vodra argued that priorities for biodefense drug development need to be established “at the highest levels of government,” not by FDA or industry. He also observed that entirely different views of incentives exist for civilian markets for drugs than do for weapon systems, for which the government assumes the economic risk and provides the incentive of the market. FDA is powerless, he argued, to lower the market risk. Shine commented that DHS legislation includes provision for an organization to set priorities as Vodra suggested. Read rejected the implication that recreating the incentives of the defense industry is appropriate and argued generally that the need is to harness the talent in the biopharmaceutical world of industry and academia. Fred Branding supported the view about the need for priorities to be set at the highest governmental level. The discussion ended with Read’s comment that “The only priority list that matters is the one that is coupled to the checkbook.”<sup>24</sup>

---

**. . . FDA is the arbiter of evidence-based information, not the generator of it—that is someone else’s responsibility.**

<sup>21</sup> Leighton Read, workshop transcript, p. 141.

<sup>22</sup> Leighton Read, workshop transcript, pp. 147–148.

<sup>23</sup> Michael Friedman, workshop transcript, p. 157.

<sup>24</sup> Leighton Read, workshop transcript, p. 164.

Three commentaries ended the afternoon discussion. Charles Ludlam, counsel to Sen. Joseph Lieberman (D-Conn.), presented an overview of the objectives, rationale, and content of legislation that was before the Senate, which steered discussion in a direction contrary to Friedman's earlier admonition to focus on FDA.<sup>25</sup> He argued that, although FDA was important, the central question is what is needed to get companies into product development. Unemployed former Soviet Union weapon scientists looking for work worldwide are a concern as they may make themselves available to rogue regimes as well as the fact that "bio-offense" is well ahead of biodefense. Current readiness is "very, very marginal." Diagnostics, Ludlam said, are sorely needed to determine who (in an attack) gets treated and who does not.

How should the government develop countermeasures? A government-led, government-funded proposal is one approach. This approach, represented in the DoD Joint Vaccine Acquisition Program, Ludlam said, is a failure and "an embarrassment."<sup>26</sup> The alternative approach is an investor and company-funded program for the biopharmaceutical sector. Tax incentives for companies without tax liability, tax credits for companies with liability, liability protection, patent protection, a guaranteed market, and a patient and long-term commitment to support these policies constitute a better approach to creating a biodefense industry and delivering government-determined target products. This approach would generate substantial work for FDA, Ludlam concluded.

Cassell commented on five items.<sup>27</sup> First, the status of countermeasures [to biological agents] involves 13 viruses on the select list of research priorities. But no other antiviral vaccines exist beyond the smallpox vaccine. Three or four antibiotics are available for bacterial pathogens, but most have been in existence for some time. Second, the needed countermeasures are broad-spectrum antivirals, broad-spectrum antibiotics, and diagnostics. But the class of broad-spectrum antibiotics that exists is quinolones, which generate resistance faster than any other class developed. In more than 40 years, only one new class of antibiotics has been developed. All of this reflects substantial technical difficulties. Third, the research effort should be supported through the National Institute of Allergy and Infectious Diseases (NIAID), in large measure because so much basic research is needed. The entire biopharmaceutical industry should be involved, not just smaller biotech companies. Fourth, the vaccine

industry is fragile; instead of the more than two dozen companies that existed in 1967, there are only four today. Realistic cost estimates and incentives to industry are needed. Finally, FDA needs added resources: In contrast to the doubling of the NIH budget and the steep increase in industry-funded research and development, FDA's budget has remained flat.

Michael Greenberger remarked that FDA is a neglected agency even to those devoting substantial attention to terrorism and counterterrorism.<sup>28</sup> The good news, he said, is the 2002 release by NIAID of a Request for Applications for regional research centers devoted to counterterrorism. An academic constituency is developing, he argued, that would drive development of countermeasures. Second, the public needs to understand that having adequate vaccines and countermeasures to bioterrorism is the functional equivalent of an antiballistic missile defense. Third, regulations would not prevent use of "any reasonably assured diagnostic or therapeutic technique," should major conflict occur. Finally, as a former regulator, though not in FDA, he cautioned that regulatory agencies are "tremendously under-resourced," which creates a serious problem.

The concluding general discussion revealed a conflict among participants over whether funding research or funding product development is the appropriate pathway to bioterrorism countermeasures that make it through FDA licensing. Will industry respond to funds expended through NIH/NIAID? That was the nub of debate.

Regarding FDA-related issues, the first question asked was whether the office headed by Andrea Meyerhoff (FDA Office of Counter-Terrorism) is adequate. One response was that it needs more resources and authority commensurate with the agency—i.e., including authority over food as well as drugs and vaccines. If leadership is to be exercised, then new resources (i.e., not reprogrammed internal resources) are needed, along with clear objectives against which progress can be measured. A policy-focused office at the Commissioner's level, not a review office, was the priority of one participant. Another asked whether there should be a new office or a new center. A new center, it was countered, would only dilute the expertise of existing centers.

The second question was whether requirements for countermeasures differ for military and civilian populations. Discussants thought the distinction unclear, even though FDA presenters had spoken of different populations. Many more similarities exist than differences, but differences involve the magnitude of the

<sup>25</sup> Charles Ludlam, workshop transcript, pp. 166–177.

<sup>26</sup> Charles Ludlam, workshop transcript, p. 169.

<sup>27</sup> Gail Cassell, workshop transcript, pp. 178–185.

<sup>28</sup> Michael Greenberger, workshop transcript, pp. 186–193.

risk between exposures on a military battlefield and those in a civilian context. It was observed that neither the public response to natural disasters nor terrorist episodes generate panic. It was also suggested that companies are reluctant to make different products for different populations. A view forcefully expressed was that one standard should exist that makes no distinctions between military and civilian populations. However, one set of standards would not rule out FDA distinctions for drug use of subpopulations.

One discussant who was involved in rewriting the DoD threat list elaborated on the difficulties that effort faced. There was a list for humans, one for animals, and another for food. Did one assume countermeasures for all? List-making depends on the answer to this question. Were delivery capabilities assumed or not? Establishing a priority list is less straightforward than might initially appear to be the case. A different point was raised that the risk of civilian attack varied as a function of where one worked and lived, a consideration that goes beyond a risk-benefit calculation for a vaccine.

## Summary Views

Javitt summarized her views in light of the day's discussion. Safety and efficacy, she suggested, are a process, not a destination, and should not be treated as static. Second, making safety and effectiveness determinations for different populations and subpopulations is not foreign to FDA. Third, the battlefield versus civilian use distinction is artificial. Fourth, regarding a new office or center, an existing infrastructure is in place, but resources, personnel, and function are unresolved. Fifth, fast-track authority currently exists, but it is unclear about how the agency might use it in relation to bioterrorism countermeasures. Sixth, in response to the concern that an interim category between IND and an approved NDA might erode public confidence in FDA's judgment, Javitt argued that the ability of the public to "understand shades of gray" should not be underestimated and that what the public does not like is being deceived. Seventh, the Orphan Drug Act could be tailored to counter terrorism. And finally, time limits on INDs raise the question of incentives for carrying early stage products through final FDA licensing.

Richard Merrill concluded the day's discussion.<sup>29</sup> He said that the issue of incentives to create a biodefense industry raised by Charles Ludlam—"a possible revolutionary reform in public funding of research and development in this area"—is one that deserves much more attention. He turned to the issues raised

by Javitt in her paper, and particularly to whether the "law is a facilitator or an impediment to FDA's performance of a heightened and possibly different set of responsibilities" in biodefense for homeland and national security. The law, he argued, should facilitate wise decisionmaking and, if it does not, changes should be made.

However, Merrill said, "an inescapable but possibly resolvable tension," exists between expectations of the defense establishment and the expectations and culture of FDA. He suggested that the Federal Food, Drug, and Cosmetic Act could be described as "designed to impede technological development." The 1938 statute inserted government review of safety, and the 1962 amendment inserted review of effectiveness between industry innovation and commercial marketing.<sup>30</sup> DoD has now come to share a common view with FDA that the medications it uses for military purposes, or that DHS uses for civilian purposes, should comply fully with FDA regulations. FDA concurs and has agreed, as Merrill put it, "to supply some lubricant" to the process. Both now speak the same vocabulary. The issue is, then, according to Merrill, "how the legal apparatus might be adjusted to facilitate the needs and expectations of the Defense Department and at the same time to remain more or less faithful to the original conception of the Food and Drug Administration."<sup>31</sup>

Three options present themselves, Merrill said. One option, presented by Javitt, are the changes FDA might consider making within its authority (or that of the Executive Branch) without requiring new authorizing legislation. The Commissioner of Food and Drugs, Merrill said, "ought to be looking for ways of interpreting existing regulations rather than changing them to facilitate performance of these functions."<sup>32</sup> A second option would be for Congress to enact legislation granting the Commissioner, or the President, authority to waive regulatory requirements for a product when he "deemed it appropriate or necessary in the national interest."<sup>33</sup> The third option would be to "recharter [FDA] to address this universe of technologies, incipient and in development for military use and national security" and to create a special unit within the agency to deal with countermeasures to bioterrorism. Each of these three options would serve as a way "for making an old and obstructive system of regulation new and flexible and encouraging of innovation," and each deserves more attention than the workshop was able to give them.

<sup>29</sup> Richard Merrill, workshop transcript, p. 222.

<sup>30</sup> Richard Merrill, workshop transcript, p. 224.

<sup>31</sup> Richard Merrill, workshop transcript, p. 225.

<sup>32</sup> Richard Merrill, workshop transcript, p. 224.

<sup>29</sup> Richard Merrill, workshop transcript, pp. 221–228.

Four issues need to be addressed within this three-option framework. First, the dichotomy between approved and investigational drugs deserves attention, including consideration of a third category. Second, regulation of manufacturing and facilities, not discussed at length, requires

attention. The third issue is whether existing authority for fast-track approvals is adequate or whether new legislation is needed. Finally, the issue of confidentiality requires discussion, since transparency of the process might provide advantages for bioterrorists. ■

---

*The workshop was supported by a generous gift from the Kaiser Foundation Health Plan.*

## Appendix: Participants

Alicea Bazzano, M.D., UCLA/RAND Corporation, Santa Monica, Calif.

Frederick H. Branding, R. Ph., J.D., Bell, Boyd & Lloyd, Chicago.

Laura Brosch, Deputy Chief of Staff for Regulatory Compliance, Lt. Col., U.S. Army Medical Research and Materiel Command, Fort Dietrich, Md.

Gail H. Cassell, Ph.D., Eli Lilly and Company, Indianapolis, Ind.

Ellen Embry, Deputy Assistant Secretary of Defense (Health Affairs), Washington, D.C.

Jeffrey K. Francer, Arnold & Porter, Washington, D.C.

Michael Friedman, M.D., Senior Vice President, Research and Development, Medical and Public Policy, Pharmacia Corporation, Peapack, N.J.

Michael Greenberg, Ph.D., J.D., RAND Corporation, Pittsburgh, Pa.

Michael Greenberger, Center for Health and Homeland Security, University of Maryland School of Law, Baltimore, Md.

Gail H. Javitt, J.D., M.P.H., Genetics and Public Policy Center, Phoebe R. Berman Bioethics Institute, Johns Hopkins University, Washington, D.C.

Anna Johnson-Winegar, Ph.D., Deputy Assistant to the Secretary of Defense (Chemical-Biological Defense), The Pentagon, Washington, D.C.

Erika King, Assistant General Counsel, PhRMA, Washington, D.C.

Charles Ludlam, Chief Counsel, Office of Sen. Joseph Lieberman (D-Conn.), Washington, D.C.

Eliot Marshall, *Science*, Washington, D.C.

Richard A. Merrill, LL.B., Daniel Caplin Professor of Law, University of Virginia, Charlottesville, Va.

Andrea Meyerhoff, M.D., Director, Office of Counter-Terrorism, Food and Drug Administration, Rockville, Md.

Dianne Murphy, M.D., Office of Counter-Terrorism and Pediatric Drug Development, CDER, FDA, Rockville, Md.

Donald L. Noah, D.V.M., M.P.H., Lt. Col., U.S. Air Force, Special Assistant for Biological Defense, Office of the Assistant Secretary of Defense for International Security Policy, The Pentagon, Washington, D.C.

Stephen D. Prior, Ph.D., National Security Health Policy Center, Potomac Institute for Policy Studies, Arlington, Va.

J. Leighton Read, M.D., General Partner, Alloy Ventures, Palo Alto, Calif.

Richard A. Rettig, Ph.D., RAND Corporation, Arlington, Va.

Kenneth I. Shine, M.D., Director, Center for Domestic and International Health Security, RAND Corporation, Arlington, Va.

John J. Smith, M.D., J.D., Department of Radiology, Massachusetts General Hospital, Boston.

Michael Stoto, Ph.D., RAND Corporation, Arlington, Va.

William W. Vodra, Arnold & Porter, Washington, D.C.

## RAND

Corporate Headquarters  
1700 Main Street  
P.O. Box 2138  
Santa Monica, CA  
90407-2138  
TEL 310.393.0411  
FAX 310.393.4818

Washington Office  
1200 South Hayes Street  
Arlington, VA 22202-5050  
TEL 703.413.1100  
FAX 703.413.8111

Pittsburgh Office  
201 North Craig Street  
Suite 202  
Pittsburgh, PA 15213-1516  
TEL 412.683.2300  
FAX 412.683.2800

New York Office  
215 Lexington Avenue  
21st Floor  
New York, NY 10016-6023  
Council for Aid to Education  
TEL 212.661.5800  
New York External Affairs  
TEL 212.661.3166  
FAX 212.661.9766

RAND-Qatar Policy Institute  
P.O. Box 23644  
Doha, Qatar  
TEL +974.492.7400  
FAX +974.492.7410

RAND Europe Headquarters  
Newtonweg 1  
2333 CP Leiden  
The Netherlands  
TEL +31.71 524.5151  
FAX +31.71 524.5191

RAND Europe—Berlin  
Uhlandstrasse 14  
10623 Berlin  
Germany  
TEL +49 (30) 31.01.91 0  
FAX +49 (30) 31.01.91 9

RAND Europe—Cambridge  
Grafton House  
64 Maids Causeway  
Cambridge CB5 8DD  
United Kingdom  
TEL +44 (1223) 353.329  
FAX +44 (1223) 358.845

[www.rand.org](http://www.rand.org)

---

The RAND Corporation is a nonprofit research organization providing objective analysis and effective solutions that address the challenges facing the public and private sectors around the world. RAND's publications do not necessarily reflect the opinions of its research clients and sponsors. RAND® is a registered trademark.