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FORCE PROTECTION: IMPROVING SAFEGUARDS FOR ADMINISTRATION OF  
INVESTIGATIONAL NEW DRUGS TO MEMBERS OF THE ARMED FORCES

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HEARING

before the

SUBCOMMITTEE ON NATIONAL SECURITY,  
VETERANS AFFAIRS, AND INTERNATIONAL  
RELATIONS

of the

COMMITTEE ON  
GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

FIRST SESSION

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TUESDAY, NOVEMBER 9, 1999

House of Representatives,  
Subcommittee on National Security, Veterans  
Affairs, and International Relations,  
Committee on Government Reform,  
Washington, DC.

The subcommittee met, pursuant to notice, at 10:10 a.m., in  
room 2154, Rayburn House Office Building, Hon. Christopher  
Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Towns, Allen, and Sanders.

Staff present: Lawrence J. Halloran, staff director and  
counsel; Robert Newman and Marcia Sayer, professional staff  
member; Jason M. Chung, clerk; David Rapallo, minority  
professional staff member; and Earley Green, minority staff  
assistant.

Mr. Shays. Good morning. I would like to call this hearing  
to order.

Under what circumstances should U.S. military personnel be  
given investigational drugs or vaccines without their consent?

The answer involves complex and controversial issues of  
medical ethics and military doctrine. Under Federal regulations  
known as the ``Common Rule,' every person asked to use an  
investigational medical product must be informed of the  
expected benefits and risks, and they must give their consent.

Prior to the Gulf war, there had been no sanctioned  
military exception to those longstanding, important informed  
consent requirements. But the threat of chemical and biological

warfare continues to force military doctors to look for new drugs and vaccines to treat or protect against exposure to unconventional weapons.

Because those medicines cannot be tested for efficacy without unethical risk to human subjects, they are considered investigational. Because the Department of Defense [DOD], considers use of investigational drugs essential treatment, not research, they see the need for waivers of informed consent requirements in deference to the demands of the battlefield.

A balance between military necessity and individual dignity is not easily struck. Experience in the Gulf war and in Bosnia remains instructive both as to the needs for waivers and the need for more rigorous standards to guide their formulation and execution. After extensive hearings on DOD's failure to provide basic information or maintain individual medical records for investigational products used in the Persian Gulf, we recommended legislation to require the President's approval for all future waivers.

Last year's Defense Authorization Act contained provisions reflecting our recommendations.

Today, we examine the President's Executive order and the Food and Drug Administration [FDA], regulation implementing that law.

New procedures and safeguards should address many of the weaknesses of the previous waiver rules. Scientific standards have been strengthened and made more explicit. Independent, nongovernment members have been added to the Institutional Review Board charged to approve and monitor waiver protocols. Subject only to security constraints, notice of waiver decisions must be published.

But protections on paper are not enough. We seek assurances from DOD that essential protections, particularly medical recordkeeping, will not be left behind again when mandatory drugs and vaccines are shipped to the battlefield. And we need to know the Department of Health and Human Services [HHS], will be vigilant in enforcing waiver conditions to protect the health and the rights of military personnel.

Our witnesses this morning bring a great depth of knowledge and many years of experience to these important questions, and we look forward very much to their testimony.

At this time, having not given the gentleman time to relax here, but we welcome you here and welcome any opening statement you would like to make.

OK. Thank you.

Well, if I could, let me just deal with our requirements to ask unanimous consent that all members of the subcommittee be permitted to place an opening statement in the record and that the record remain open for 3 days for that purpose. Without objection, so ordered.

And I ask further unanimous consent that all Members be permitted to include their written statement in the record. Without objection, so ordered. And to inform our witnesses that their statements clearly will be part of the record and would welcome them making any point they want that may be even in addition to their statement for the record.

[The prepared statement of Hon. Christopher Shays follows:]

[GRAPHIC] [TIFF OMITTED] T4776.001

Mr. Shays. At this time, we have three witnesses: John Spotila, Administrator, Office of Information and Regulatory Affairs, Office of Management and Budget, and he'll speak

first. Then we have Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs, Department of Defense. And then we have William Raub, Dr. William Raub, Deputy Assistant Secretary of Science Policy, Department of Health and Human Services.

So we have three excellent witnesses that will be able to help us sort this issue out, and I would invite them to stand so we could administer the oath which we do in this committee to all witnesses who testify.

[Witnesses sworn.]

Mr. Shays. Thank you. Note for the record that all three witnesses responded in the affirmative to the oath, and we'll start with OMB.

What we do with our clock is we turn it on for 5 minutes. You're allowed to go over, but we want you to be as close to 5 as you want; and, after 10, the gavel goes down hard. Hopefully, we don't get to 10.

STATEMENTS OF JOHN SPOTILA, ADMINISTRATOR, OFFICE OF INFORMATION AND REGULATORY AFFAIRS, OFFICE OF MANAGEMENT AND BUDGET; SUE BAILEY, ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS, DEPARTMENT OF DEFENSE; AND WILLIAM RAUB, DEPUTY ASSISTANT SECRETARY, SCIENCE POLICY, HEALTH AND HUMAN SERVICES

Mr. Spotila. Good morning, Chairman Shays and members of the subcommittee. Thank you for inviting me here today to discuss Executive Order 13139 which represents a thoughtful effort to implement the Strom Thurmond National Defense Authorization Act for fiscal year 1999. We appreciate your strong, continuing interest in protecting the health of our military personnel.

Before discussing the order in detail, let me summarize the events leading to its issuance.

Prior to the Persian Gulf war, the Department of Defense concluded that Iraq had chemical and biological agents that posed great risk for our deploying troops. DOD identified specific drugs that could counter the effects of these agents, but the drugs were not yet approved by the FDA for that specific use.

For the Gulf war, FDA granted DOD waivers of the need to obtain informed consent for the use of two such drugs, PB, potentially useful against nerve gases, and bot tox, a vaccine against botulism. My understanding is that DOD only implemented the waiver for PB.

In evaluating the use of this waiver during the Gulf war, we learned many lessons. In 1997, FDA sought public comment on whether its rule permitting military waivers of informed consent should be revoked or revised. FDA submitted a revised rule to OMB on this subject in June 1998, leading the administration to initiate an interagency process to develop a coordinated policy on this issue.

Meanwhile, Congress acted to ensure that DOD would have a modified mechanism to request waivers of informed consent. Section 1107 of the 1999 Defense Authorization Act gave to the President authority to grant waivers of informed consent upon a request from the Secretary of Defense if the President finds that obtaining informed consent is not feasible or is contrary to the best interest of the military member or is not in the interests of national security.

To implement this act and after reviewing the results of the interagency process coordinated by OMB, the President signed Executive Order 13139. The order establishes new

procedures for the consideration of a DOD waiver request and is supplemented by a companion FDA rule establishing the standards and criteria that the President will apply in making the waiver determination.

The President has decided to apply these standards and criteria, even in the national security area, as further protection for our troops.

Both the order and the rule reflect a consensus reached by all of the relevant agencies on the best means of implementing the act.

Our policy continues to be that the U.S. Government normally will only administer products approved for their intended use by FDA. In what we hope will be very limited circumstances, however, protection of our deployed military personnel may require use of an investigational drug. Even in most of those situations, DOD would administer such products with the consent of the individual military member.

Under certain rare circumstances, however, and with strict controls, it may need to administer such products without obtaining an individual's consent in order to preserve military capability in a particular operation and to protect the health and well-being of our deployed troops. It is only under these limited circumstances that DOD would seek a waiver, and the President would grant it only when necessary.

The order establishes a process for waiver decisions to be carefully evaluated in a timely manner and used only when absolutely necessary, creates multiple layers of oversight to ensure accountability and proper safeguards for military troops and builds in additional procedures and safeguards to protect the health and well-being of our military troops prior to, during and after a particular military operation.

When the Secretary of Defense makes a waiver request, it must contain a full description of the threat, written documentation that the Secretary has complied with each of FDA's standards and criteria and additional pertinent information. To ensure that FDA is brought into the decisionmaking process early, the Secretary must develop the waiver request in consultation with FDA. Before a waiver request can be made, an Institutional Review Board must review DOD's protocols for military use of investigational drugs.

The FDA Commissioner must certify to the President's national security and science advisers whether FDA's standards and criteria have been adequately addressed and whether the investigational new drug protocol should proceed. The Commissioner will base this certification on a complete assessment of the criteria specified in the rule, including FDA's own analysis of the safety and effectiveness of the investigational drug in relation to the medical risk that could be encountered.

The President's national security and science advisers then carefully review the submission and prepare a joint advisory opinion for the President, recommending whether the waiver of informed consent should be granted. The President then will approve or deny the waiver request.

If a waiver request is granted, the DOD offices implementing the waiver, DOD's Inspector General and the FDA all conduct review and monitoring to assess whether DOD continues to meet the standards and criteria. DOD must report any changed circumstances to the President and must comply with any additional reporting requirements that the President specifies at the time of approval.

To increase public accountability, the act also requires the Secretary to notify the congressional defense committees and the public that a waiver has been granted.

As further protection for our troops, the order requires DOD to provide training and health risk communication on the requirements of using an investigational drug in support of a military operation to all military personnel, including those in leadership positions. In the event that DOD requests a waiver, DOD must submit its training and health risk communication plans to FDA and the reviewing IRB.

These steps seek to ensure that all military personnel required to take the investigational drug are fully informed.

Finally, the order places a time limit on the waiver. It will expire at the end of 1 year or less as specified by the President. If the Secretary seeks to renew a waiver prior to its expiration, the Secretary must submit to the President an updated request and must satisfy all of the criteria for a waiver. The President may also revoke the waiver based on changed circumstances or for any other reason at any time.

The order seeks to minimize the need for waivers. It directs DOD to collect intelligence in advance on potential health threats that may be encountered in an area of operation and to work with HHS to ensure that appropriate counter measures are developed. DOD will study these potential products to determine whether each is safe and effective for its intended use.

Both Departments have committed to a collaborative effort to speed up the drug approval process, further minimizing the need for such a waiver in the future. These are all positive steps for protecting the health of our military personnel.

We hope that DOD will not need to invoke the waiver procedure at all in the future. If it does find it necessary, however, the order, combined with FDA's new interim final rule, will significantly improve the safeguards necessary to protect the health of our military personnel.

Thank you for the opportunity to discuss the administration's efforts in this area. I would be pleased to answer any questions you may have.

Mr. Shays. Thank you.

[The prepared statement of Mr. Spotila follows:]

[GRAPHIC] [TIFF OMITTED] T4776.002

[GRAPHIC] [TIFF OMITTED] T4776.003

[GRAPHIC] [TIFF OMITTED] T4776.004

[GRAPHIC] [TIFF OMITTED] T4776.005

[GRAPHIC] [TIFF OMITTED] T4776.006

Mr. Shays. Dr. Bailey.

Dr. Bailey. Congressman Shays, members of the committee, I am happy to be here today to discuss the Executive order.

You know, we are obligated to provide the best protection we are capable of in providing our troops protection against chemical and biological warfare. The United States today faces the monumental challenge of establishing quickly a credible medical defense against these weapons. Unfortunately, for most chemical and biological agents such as soman, plague, tourilinea, botulinum and other toxins and bioengineered substances there are not yet available, effective FDA-approved

prevention or treatment products.

Research, development and production of such products will take, in fact, many years, even with FDA's commendable new animal efficacy rules.

The Department is committed to moving IND products to licensure as quickly and efficiently as possible. In the meantime, however, the best medical judgments available will demand the use of some products classified by the FDA as investigational. When an investigational product is the only means available to protect against a lethal chemical or biological weapon, the lives of individual members, the safety of their comrades who rely on them and the success of the military mission require a uniform use of that medical protection.

DOD believes that the President must be given a range of options, including the feasible use of these investigational products for providing credible medical protection against chemical biological weapons. The Executive order provides the President with that framework and the flexibility, when essential, to waive informed consent. DOD will be working closely, interagency with FDA, to develop the appropriate protocol and procedures to enforce this new Executive order.

Thank you.

Mr. Shays. Thank you.

[The prepared statement of Ms. Bailey follows:]

[GRAPHIC] [TIFF OMITTED] T4776.007

[GRAPHIC] [TIFF OMITTED] T4776.008

[GRAPHIC] [TIFF OMITTED] T4776.009

[GRAPHIC] [TIFF OMITTED] T4776.010

[GRAPHIC] [TIFF OMITTED] T4776.011

[GRAPHIC] [TIFF OMITTED] T4776.012

[GRAPHIC] [TIFF OMITTED] T4776.013

[GRAPHIC] [TIFF OMITTED] T4776.014

Mr. Shays. Dr. Raub.

Mr. Raub. Mr. Chairman, with your permission, I will make a short statement now and ask that my long statement be submitted to the record.

Mr. Shays. That's fine.

Mr. Raub. Good morning, Mr. Chairman, Mr. Sanders. I am William F. Raub, Deputy Assistant Secretary for Science Policy at the Department of Health and Human Services.

I appreciate this opportunity to discuss policies governing the administration of investigational medical products to U.S. military personnel, in particular the safeguards included in President Clinton's Executive Order 13139 and the new Food and Drug Administration interim rule on waiver of informed consent.

Protection of individuals receiving health care services, including those receiving investigational products, is of paramount concern to HHS, as evinced by its position on the Patient Bill of Rights, medical data privacy, and the allocation of human organs for transplantation. HHS believes that exceptions for informed consent should apply rarely. We believe that the President's Executive order and the new FDA



interim rule provide a sound framework for addressing exceptional circumstances arising in the context of military options.

Normally, before a sponsor can initiate clinical testing of an unapproved product or an approved product intended for a new use, an investigational new drug application must be filed with FDA. The IND application format calls for information that is pertinent to protecting the rights and safety of human research subjects, including the requirement for obtaining their written informed consent.

In December 1990, motivated by concerns about potential chemical and biological threats to troops participating in Operation Desert Storm, the Department of Defense requested that FDA waive the informed consent requirement for use of particular investigational products. In response, FDA published an interim rule amending its informed consent regulations such that the Commissioner of Food and Drugs, given appropriate evidence, could determine that obtaining informed consent from military personnel for use of a specific investigational product would not be feasible in certain circumstances and to grant a waiver from the requirement for obtaining consent.

Shortly thereafter, the Commissioner approved waiver requests from DOD for use of pyridostigmine bromide tablets and botulinum toxoid vaccine. The aftermath of these decisions has been subject to intensive examination. The President's Advisory Committee on Gulf War Veterans' Illness, deliberating during 1996 and 1997, described a number of shortcomings in DOD use of investigational products during the Persian Gulf war and recommended that FDA revisit the interim rule to address, among other things, the adequacy of information disclosure to service personnel, recordkeeping and long-term followup of individuals who received investigational products. An independent evaluation by FDA identified significant deviations from applicable regulations.

In July 1997, FDA published a request for comments on the 1990 interim rule. The responses pointed out significant areas that needed to be strengthened, including the following: Provision of information about an investigational product before its use; followup to assess whether adverse health consequences ensue from use of the investigational product, and if so, to determine their nature and extent; oversight and accountability when investigational products are used; and involvement of non-DOD personnel in decisions to use investigational products without informed consent. All of these topics are covered in the new FDA interim rule.

The Strom Thurmond National Defense Authorization Act answered in the affirmative the question of whether waiver of informed consent in military operations ever is appropriate. As a consequence of that statute, only the President may waive the informed consent requirement for military personnel engaged in particular military operations. Moreover, he may make such a waiver only if he determines in writing that obtaining consent is not feasible, is contrary to the best interest of the military member or is not in the interest of national security.

If his determination be based on grounds that it is infeasible or contrary to the best interest of the military member, the President must apply the standards and criteria set forth in the new FDA interim rule.

On October 5, 1999, FDA published the new interim rule. It requires the Secretary of Defense to certify and document to the President that the standards and criteria in the rule have

been met, including, one, that the medical risk that could be encountered during the military operation is outweighed by the expected benefits of the investigational product; two, that military personnel may be subject to a chemical, biological, nuclear or other exposure likely to produce death or serious injuries; and, three, that a satisfactory alternative therapeutic or preventive treatment is not available and that voluntary participation could significantly risk the health of individual service members and threaten the military mission.

The interim rule also requires that each member involved in the military operation be given, prior to the administration of the investigational product, a written information sheet including information on the investigational product, the risks and benefits of its use, potential side effects and other information about the appropriate use of the product; that DOD provide, consistent with classification requirements, public notice in the Federal Register describing each Presidential determination to waive informed consent, a summary of current scientific information on the product or products involved, and other pertinent information; and that DOD train medical personnel and potential recipients regarding the specific investigational product prior to its use.

Further, DOD must certify and document that it will provide adequate followup to identify and assess beneficial or adverse health consequences that result from the use of the product and that it is pursuing drug development and marketing approval for the investigational product with due diligence. And the new interim rule provides for FDA to complete its review of the proposed protocol for use of the investigational product before that protocol may be implemented.

FDA also can contribute in other ways to DOD's mandate to protect military personnel from medical risks associated with military operations. FDA is collaborating with DOD in its efforts to develop approved products for military need, thereby obviating the need to use these products while they are still in the investigational stage.

Also, mindful that the traditional efficacy studies sometimes are not feasible or cannot be conducted ethically with human research subjects, FDA recently issued a public comment a proposed rule that would allow the use of animal testing data as the primary basis for human products approval under carefully limited circumstances.

Mr. Chairman, HHS learned important lessons from its experience with the waiver of informed consent during the Persian Gulf war, and we are putting those lessons to work as we prepare for future exigencies, both military and domestic.

I will be pleased to respond as best I can to whatever questions you may have.

Mr. Shays. Thank you.

[The prepared statement of Mr. Raub follows:]

[GRAPHIC] [TIFF OMITTED] T4776.016

[GRAPHIC] [TIFF OMITTED] T4776.017

[GRAPHIC] [TIFF OMITTED] T4776.018

[GRAPHIC] [TIFF OMITTED] T4776.019

[GRAPHIC] [TIFF OMITTED] T4776.020

[GRAPHIC] [TIFF OMITTED] T4776.021

[GRAPHIC] [TIFF OMITTED] T4776.022

[GRAPHIC] [TIFF OMITTED] T4776.023

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[GRAPHIC] [TIFF OMITTED] T4776.026

[GRAPHIC] [TIFF OMITTED] T4776.027

[GRAPHIC] [TIFF OMITTED] T4776.028

[GRAPHIC] [TIFF OMITTED] T4776.029

[GRAPHIC] [TIFF OMITTED] T4776.030

[GRAPHIC] [TIFF OMITTED] T4776.031

[GRAPHIC] [TIFF OMITTED] T4776.032

[GRAPHIC] [TIFF OMITTED] T4776.033

[GRAPHIC] [TIFF OMITTED] T4776.034

Mr. Shays. Mr. Sanders.

Mr. Sanders. Thank you, Mr. Chairman. I'm going to have to apologize because there's a markup down the hall in the Banking Committee that I have got to be involved in.

I applaud you for holding this important hearing. I have long been concerned about pyridostigmine bromide, the possible impact this had on Gulf war illness, the role of DOD, informed consent and so forth and so on. I will be back as soon as I can, but I just want to thank our guests for being with us today, and I will try to be back as soon as I can.

Mr. Shays. Thank you, Mr. Sanders.

Mr. Spotila, according to your testimony, you said U.S. policy is that it will only administer products approved for their intended use by FDA and that only in very rare circumstances will deployed military personnel be given investigational products. You also said in most of these situations informed consent will be obtained. And you also said, to further narrow the use of waivers, and I am not doing a direct quote, the Executive order also commits the President to consider FDA standards and criteria even when deciding on waivers requested solely on national security grounds. I have a number of questions I want to ask you regarding this.

How does the Executive order ensure use of investigational products by DOD will in fact be rare?

Mr. Spotila. There are two aspects of that, Mr. Chairman. It sets the policy that you have actually quoted from my testimony, that we should use these as rarely as possible and we should do it only with the health of our troops and the security of our country as the guiding principle.

From an oversight standpoint, OMB works with the Department of Defense and with FDA as needed to coordinate the process of implementing this Executive order. We have obviously a responsibility on the part of those particular departments to carry out the policy that the President has set. When we're

dealing with investigational drugs, the general rule is that informed consent is needed, and in the event that the Secretary of Defense feels that a waiver of informed consent is appropriate, then the procedures described in the order would go into effect and need to be complied with.

Mr. Shays. How do you--and I'm going to be asking you basically five questions and then, Dr. Bailey, Dr. Raub, I'd be happy to have you respond to any of the questions that I have asked.

How do you reconcile the apparent conflict between a policy that requires informed consent and the military policy that appears to require mandatory, universal use of every investigational product for force protection?

Mr. Spotila. I'm not sure if I'm following your question, Mr. Chairman.

Mr. Shays. Well, I guess the bottom line is, there's a gigantic conflict between informed consent and the military policy that requires mandatory universal use, and I don't see how we're going to reconcile that. I mean, I'm responding really to the concept that it is going to be rare. I don't think it is going to be rare. We're in a whole new world right now.

Mr. Spotila. It is difficult to tell how rare it would be, because it is difficult to know what the threat is. If the threat is greater, then we may be faced with more of these circumstances.

When drugs are approved, of course, DOD has always been able to require their mandatory administration. All servicemen receive shots. We all know that. When the drug is investigational, then we're in a different situation, and there either informed consent is needed or a waiver must be obtained. We would hope that we don't have a great need for this or won't go forward, but we have to be prepared for the contingency.

Mr. Shays. I guess really what I'm focused on is that either the requests are going to be rare or the requests won't be, but the granting of those requests will be rare. I happen not to believe--I happen to believe the requests will not be rare. I think they will be coming quite often. So I then make an assumption that you believe that these requests will be denied.

Mr. Spotila. We would hope that the safeguards and the procedures that are set forth in the order which require review at several different levels, including close coordination with the FDA and then a review by the President's national security and science advisers, that all of these steps will reduce greatly the possibility that a request will actually get to the President that is not well supported. The President certainly reserves his authority not to grant a request once it comes to him for a waiver of informed consent.

Mr. Shays. Thank you. How would the President know whether DOD is complying with the terms and conditions of a waiver such as recordkeeping and adverse event reporting?

Mr. Spotila. He will rely on the Secretary of Defense to comply with his responsibilities, with FDA to comply with its responsibilities and I'm sure with OMB to use its oversight role. We have built in a number of levels of safeguard and monitoring. We note that the Department of Defense Inspector General, for example, as I indicated in my testimony, will also be involved in oversight. So the President is really going to rely on these oversight mechanisms.

Mr. Shays. Under the Executive order, what indicators would

the President need to see to be persuaded DOD has pursued research and full FDA approval of an investigational product and not delayed expensive clinical studies knowing the waiver process would be available on the eve of war?

Mr. Spotila. He will rely on the certifications he receives and the recommendations of his own advisers, his national security and science advisers in assessing what DOD has done and whether it's sufficient.

The real key is that, certainly from our standpoint, that this work be done in advance so that the President is not put in the difficult position of facing the need to administer a drug when work has not been done in advance, work that perhaps should have been for the protection of our troops. Ultimately, he's going to make the decision he has to make, but we all certainly feel a responsibility to work with DOD and FDA to try to make sure that they do plan in advance and reduce the number of instances where this might occur.

It's also important to recognize that FDA is playing a large role in this; this is appropriate given their area of responsibilities and expertise.

Mr. Shays. My sense was, though, in previous hearings that we've had, that basically FDA washes their hands of any obligation once they allow, for instance--I don't have this sense that they feel they have any real responsibility once they have allowed DOD to use an investigational drug.

Mr. Spotila. Under the Executive order they have a greater responsibility perhaps than they have exercised in previous circumstances, but I certainly would defer to Dr. Raub to discuss more specifically how FDA views its ability to help in this area.

Mr. Shays. I'd invite Dr. Bailey or Dr. Raub to respond to any of the questions I have asked. Dr. Bailey.

Dr. Bailey. Well, in regard to how often it would occur, I would sincerely hope, and I know the Department hopes, that this request for a waiver, which by the way can only be made by the Secretary of Defense, the original request, would be very, very rare. Unfortunately, you know that potential adversaries, perhaps as many as 10 or 12, are engaged in development of or have weapons for which we have no other defense but to use or to request a waiver for the use of an investigational product being it is the only pretreatment that could save lives.

Mr. Shays. Right. Given the threat out there, given the lack of research we have done to provide our soldiers, our sailors, our marines, our air force with the kind of protection I think DOD envisions, I envision a lot of requests being made for off use of various drugs and that it won't be rare. I see that happening, but I could be wrong.

Dr. Bailey. Well, I think if we look at the No. 1 threat at this point, which is anthrax, that is not an investigational new product. Fortunately, that is an FDA licensed product that has been licensed for many, many years. Furthermore--so anthrax would be one of our major weapons of mass destruction that we are looking for protection for our troops in terms of medical vaccine.

In terms of pretreatment and investigational new drugs, most investigational new drugs are, in fact, not mandatory and are under research and are working toward full licensure. We also--we look at pyridostigmine, we have \$20 million--almost \$20 million worth of research ongoing and are continuing to look at safety and efficacy of that pretreatment, but, again, keeping in mind that it is the only pretreatment that could

save the lives of our troops were they exposed to soman.

Mr. Shays. Do you want to make a comment, Mr. Raub?

Mr. Raub. Just several comments, Mr. Chairman, one on the issue of the likelihood that requests will be rare and approvals rare as well. I think we need to keep in mind that, by definition, this could not cover all investigational products in that they cover a considerable spectrum from some of the very first uses in human subjects through products that are well along in clinical development. The standards----

Mr. Shays. I'm sorry, you lost me in the first part. What's your point? I'm sorry.

Mr. Raub. Well, there's what I'll call a maturity or a ripeness of an investigational product, that something can be labeled investigational product but only have just begun in human testing, and, therefore, there is enough evidence of efficacy to make it a plausible candidate for this; whereas other investigational products may have been several years in development, and there'd be a much richer set of information for the Secretary of Defense and the Commissioner of Food and Drug to consider. So there's quite a spectrum of the state of development of investigational products.

Mr. Shays. Right. And so what's the point, though?

Mr. Raub. Well, the point is, I think you had expressed the concern that this sort of mandated the use of all investigational products, and I was just clarifying that it's only investigational products that are indeed far enough along in development to have a plausible basis of being efficacious.

Mr. Shays. So your sense is that only the mature ones will be given that waiver?

Mr. Raub. Yes, sir, and I say that because my second point, the FDA interim rule lays out 18 different conditions that must be fulfilled and certified and documented on this. I view that as a quite formidable gauntlet to be run for these products.

Mr. Shays. In order to be granted a waiver?

Mr. Raub. To be granted a waiver, yes, sir.

Mr. Shays. Any other responses?

Dr. Bailey. I would also like to add that the use in military exigencies, tick-borne encephalitis is another example of an IND where DOD did not request a waiver of informed consent. When we are looking to use an investigational new drug, if it is something that can be done ahead of time, not in that exigency moment, in fact we will not look for a waiver. We will make every effort to obtain appropriate informed consent and to work within the protocol as dictated by the FDA.

Specifically, though, again, when we are faced with a product, a weapon of mass destruction such as soman for which there's no other treatment, that is the situation in which, were our intel to indicate--confirmed intelligence were to indicate soman in theater on the battlefield, that is a time where we may be faced with having to request a waiver, but I see that as being a very rare situation, and I think our TBE, tick-borne encephalitis, situation indicates our real desire to work either with FDA-licensed products or to work within the standards for INDs.

Mr. Shays. OK. Even though I'm not sure how much I want to take the committee's time to go down the whole anthrax issue, but, bottom line, we were using it for a particular use with potentially about 300 people a year, and DOD decided to use it, administer it to potentially 2 million of our American soldiers, sailors, marines and air force, as an antidote to military use, presenting itself very differently than it would

present itself to the 300 who traditionally would get it every year, airborne versus----

Dr. Bailey. Cutaneous. Well, let me just speak very briefly to that. Because I agree that's a whole other hearing, but in fact we again have studied--and we must, I think, delineate for this hearing that the anthrax vaccine is a licensed vaccine. Yes, it was used for myasthenia gravis over the years, but we also have used it with our researchers for years in Fort Detrick.

And, furthermore, I want to quote from March 13, 1997, when Michael Friedman--Dr. Michael Friedman spoke from HHS, saying that as far as the issue about cutaneous versus inhalation, we know that our product is effective in Rhesus monkeys against--90 percent effective, 90 to 95 percent effective against inhalation anthrax, and again where our troop is exposed it is virtually 100 percent deadly were they not protected with the vaccine.

Mr. Shays. I just want to say you keep making that point, and that's why I question about the requests will be rare. I could give you and you could give me potentially 50 biological agents that could be that kind of threat, and then you will try to find an antidote to each one. I'm sorry. That doesn't make me feel it's going to be rare. I am not saying--I am raising the question of whether the requests will be rare and whether the granting of the waiver will be rare, and my only issue is with the concept that I should feel comfortable that it will be rare. I don't think it will be, but time will tell.

Dr. Bailey. Mr. Chairman, could I just add to the last point that you had brought up about the cutaneous versus the inhalation? In that March 1997, letter, the HHS stated results from animal challenge studies have also indicated that preexposure, administration of anthrax protects against inhalation anthrax. So we feel we're comfortable with that particular vaccine which is not an IND and, of course, would not involve a waiver.

Specifically about looking at it in rare instances, it is the rare instance where we would be faced with not only any CBW, any chemical biological warfare agent, but specifically soman in the case of PB, an investigational product. That is hopefully something we will not be encountering in the future, and it would be a very rare instance where we would have to look for a waiver and informed consent, and I would hope by that time we would have it licensed for this use.

Mr. Shays. Thank you.

Mr. Allen.

Mr. Allen. Thank you. Thank you all for being here. I regret that I only have a few minutes. I am sort of running between one thing and another.

But, Dr. Bailey, I have--I want to take you back. This may seem a little bit off the point of what we're discussing today, but I assure you I'm going to bring it back.

In your--in previous testimony before--before this committee, I believe, you indicated that with respect to the anthrax vaccine there was no evidence of anaphylactic reactions to that vaccine. Our sources at Dover Air Force Base tell us there are 64--at least 64 cases of anaphylactic reactions and--but that these severe reactions are not being described, reported, brought to the attention of the appropriate officials.

Second point that we're hearing is that troops with reactions initially were sent to Walter Reed for further study

where they could receive a 1-year waiver from vaccination if doctors agreed that they had had a severe reaction. However, that policy was changed to refer them instead to Andrews Air Force Base where the perception is service members are much less likely to get a 1-year waiver because it is an air base with a military mission and not a military hospital with a medical mission.

In March--you testified before the subcommittee in March that you had seen no evidence of severe reactions to the vaccine. Have you learned anything either related to Dover or anywhere else in the country that would change your testimony?

Dr. Bailey. Well, first of all, the reporting is done through the vaccine adverse event reporting system, which is part of CDC. That is true for all vaccines, and that is the reporting system we are using with the anthrax vaccine program. The specific referral to anthrax or to anaphylactic reaction should have been related to the outcome of death in regard to an anaphylactic toxic reaction. Specifically----

Mr. Allen. I understood the word meant a severe or systemic reaction.

Dr. Bailey. It does. It can lead to death. My referral was fortunately in our program, as opposed to other programs and other vaccines, where unfortunately occasionally you have an anaphylactic reaction that results in death. That has not occurred--we have had no deaths in a program which now includes over 340,000 troops and over a million doses of vaccine administered. So, again, we feel it is very safe.

Now, we do report through VAERS, and at this point, we have somewhat over 300 reports to VAERS, that's the vaccine adverse reaction reporting system, and--but only about 20 of those are the severe type that would require hospitalization or a loss of duty time. I think the main message would be that the adverse reactions we are seeing are mostly localized and are very much in line with the vaccines that are given here in this country to children or typhoid, tetanus, diphtheria, the kinds of reactions we see with other vaccines.

Anthrax also does have some reactions, but they are very much in line with all other vaccines that are given.

Mr. Allen. Let me sort of come from that to--I'm sorry, I can't recall who was testifying, but it was a hearing on--before the Armed Services Committee on which I also sit, and the military brass was lined up at the table, and the question was posed whether or not there were some national system for tracking adverse reactions to the anthrax vaccine. And the response was no, and we don't want to do it essentially because we don't do it for any other vaccine, and that--I wish I could cite you chapter and verse, but that was the response that was fairly uniform among the three or four military officers who were testifying at that hearing, and I didn't come prepared with it.

So here's my question. How would--and you can correct me on that if you'd like--but what I'm leading to is, how would DOD monitor adverse reactions in a comprehensive way the service members may experience as a result of taking an investigational drug? I will tell you as a Member of Congress sitting here listening to what I've heard at the various hearings I have been to, it's hard for me to have confidence that the military's really committed to a thorough reporting of adverse reactions, and I'll dump all of that in your lap for your response.

Dr. Bailey. OK. First, let me say I've had five anthrax



shots, and I can punch in on the computer at the Pentagon or I have done it out in the desert under a tent in the Persian Gulf, said--put my name in, put in my Social Security number and see what comes up. It tells exactly how many I've had and when my next one is due, and it will tell me if I'm late by 2 weeks. So we have a very, very specific tracking system.

As part of the tracking----

Mr. Allen. Wait a minute. That's totally different from whether you're actually accumulating information in Washington about adverse reactions.

Dr. Bailey. OK. I would also add, first of all, in regard to your first statement about remembering what happened and the first answer that was given, I believe what you're referring to is the refusal policy. Because that is something that I do recall that the services, each of them testified that that is not something that is done for any order or any vaccine, and that is what they are not tracking.

What I'm trying to indicate to you is that we are tracking very specifically all of the anthrax immunizations, and we clearly do want to look for adverse reactions. In fact, we have a project at Tripler involving about 600 people who are all medics themselves or health care administrators that specifically ask for any adverse reaction. If it's an ingrown toenail and you think it's not related to this vaccine, we still want to know any medical problem you have. That is going after those adverse reactions in a very constructive way.

We also are specifically part of the same program that all vaccines participate in in VAERS with CDC. So we are aggressively tracking this and look with our information systems to even better products that will allow us even greater clinical knowledge about the vaccines we give.

Mr. Allen. So are you confident that you have access--you can now say there are 20 or however many cases of severe, systemic reactions to the anthrax vaccine, and when you give that number, are you confident that you've got all the cases?

Dr. Bailey. I will provide for the record the specific number and--but, yes, I am confident in our ability to track adverse reactions.

Mr. Allen. Thank you.

Thank you, Mr. Chairman.

Mr. Shays. Thank you.

I'd be happy to recognize Mr. Towns, who is my former ranking member, and I miss him a lot.

Mr. Towns. Thank you very much. Thank you, Mr. Chairman, and also, let me thank all of you for your testimony.

You know, I have got sort of basic kinds of questions. How would DOD ensure that the service members receive the proper dosages of investigational drugs in a timely manner? I mean, how? Could you assure me of that?

You, Ms. Bailey, go ahead. It's fine.

Dr. Bailey. Dr. Bailey.

Mr. Towns. Dr. Bailey, I'm sorry.

Dr. Bailey. In fact, it may be helpful for you to know some of the changes we've made in one of the investigational new drugs that we are all focused on, and that is pyridostigmine. During the Gulf war we gave out pyridostigmine which had to be given at least 8 hours before an attack. Again, soman is a deadly, lethal agent, and had we not provided a pretreatment, our usual medications, our medics were not able to provide any treatment that would have saved the lives of our troops. So we had to use pyridostigmine.

It was specifically given in a--in this packet form, and the directions for use said: Commence taking only when ordered by your commander, take one every 8 hours, and it is dangerous to receive the stated dose.

Now, the problem was that I think now, in retrospect, we all realize that was not enough information in this format. We did have other information provided through commanders' calls and that was the line responsibility. But at this time I would like to report that in fact we have changed what the packet includes, and the packet now includes the same information I stated before, but it also has on the back, and I just, because this I think is very essential to what we're talking about, would read to you that it has warnings about if you have asthma, for instance, or are pregnant or taking medicine for high blood pressure, you would see your unit doctor before taking pyridostigmine.

It also says that PB is for military use only. It is not approved by the FDA for marketing as a poison gas antidote and before using read the enclosed information, and there is an entire insert which has much more information about the effects, about warnings, about when not to take PB, how specifically to take it and other information about the drug. So we feel that plus the warnings that are on the record will allow us to have better information to the troops.

Mr. Shays. Would you submit those for the record, please?

Dr. Bailey. I will get you those for the record, sir.

Mr. Shays. Also, the study, Tripler study, when will that be available?

Dr. Bailey. That is an ongoing study. It is ongoing as we speak looking at those adverse effects, and I will get you that as well.

Mr. Shays. Thank you very much.

Mr. Towns. Let me say--and I'm sure you've probably heard it even more than I have heard it. What people are generally saying is that this is really research going on and that the physicians who are involved in it, that they're so wrapped up in their research that sometimes they're not looking at the day-to-day conditions of the patient in terms of how the patient's condition is changing, whatever, and that the structure is bad, that you need to have a physician that's just going to look at the patient in terms of the patient's reaction. Because what they're saying, and I know you've heard it, that the doctor is so involved in the research aspects, because this thing is research and, of course, you need to have somebody else to look at the other aspects, because if I'm involved in the research, I'm more attuned to that, then that's what I'm interested in, and sometimes I might forget some other things, and there needs to be someone to look at the day-to-day activities of the patient in terms of whether they're responding, what kind of way, and so there's a lot of criticism about the structure. Could you respond to that? Anybody, anybody.

Dr. Bailey. Well, I can assure you that this is not research, that the use of this investigational new drug as a pretreatment for the nerve gas soman will only be used in those rare circumstances where we have no other method for protecting the life of the troop member. It is not research. Research generally implies that you're looking for licensure for another----

Mr. Towns. You have heard this comment, haven't you?

Dr. Bailey. Yes, and I understand what you are saying, and

I would just assure you that our medics, our physicians, our medics in the field, it is their prime responsibility to provide force health protection, and we in health affairs, even while we are doing policy, are aware of our responsibility to that mission, not to the mission of research.

I would also add that we do have oversight by the Armed Forces Epidemiologic Board which makes recommendations to me and to the Surgeons General, and that is a civilian oversight board. We often also involve the Institute of Medicine, as you know, the President's advisory committee. So there are many civilian oversight organizations that provide us with I believe the kind of medical oversight that you would be more comfortable with.

Mr. Raub. Mr. Towns, might I just add, make it more broadly? I, too, have heard the comments. I believe they may be based in part on a less than full appreciation of the safeguards already in place or the ones more recently put into place as a result of the Executive order and FDA's new interim rule. For example, many products are under development by the Department of Defense as investigational products, and are subject to all of the requirements of FDA for investigational products, including informed consent, and so there are mechanisms within the Department of Defense as well as the FDA governing those, and those don't change.

In those instances where, under the new rules, the President approves an investigational product for use without informed consent as a basis of either therapy or prevention, as I indicated in my earlier comment to the chairman, I believe the conditions are so specific and so stringent that nothing approaching a frivolous or overambitious use of that product could pass. And I don't believe the Department of Defense would in fact propose such.

So we are confident. We believe we need to work harder to ensure that people understand the nature and the strength of the protections that are in place.

Mr. Towns. Thank you very much.

You want to add anything there?

Mr. Spotila. No. I think that I would agree completely with Dr. Raub's and Dr. Bailey's treatment of this.

Mr. Towns. I want to understand one thing very clearly, how this new system will work in practice, especially when things get hectic in a wartime situation where things are really hectic. Under this process, it appears DOD is supposed to develop a waiver request in consultation with FDA. You know, what does this really mean? What does it really mean?

Mr. Spotila. The President has directed that FDA be involved in the preparation of the waiver request precisely so that it can proceed more quickly and so that it can be coordinated more closely with FDA's traditional oversight of the use of investigational drugs. That is a recognition that time could be a factor. And so the order directs DOD to be looking farther out in advance both from an intelligence standpoint and from a development of new products standpoint, so that we don't find ourselves at the last minute having to make decisions. And then in setting up the particular process for a waiver request, it involves FDA at a very early stage and throughout the proceedings precisely so we get their input and so that the President can be as well informed as possible before making any decision about a waiver of informed consent.

Mr. Towns. Go ahead.

Dr. Bailey. I may have more information than you would want

to know, but you can stop me at any point. And let me say, we are in the process, first of all, of developing this protocol. Now that the Executive order is in place, we're working, interagency, all of us, to develop a protocol that will adhere to the criteria which is appropriate.

Specifically, we're adding information on the Executive order to all of our training classes, our pamphlets, our manuals and other publications that are currently provided on chemical biological countermeasures. That will assure that the military personnel receive as part of their CBW training information on the reasons why INDs are used and may be needed. We are adding information to the medical providers and training classes as well, to their pamphlets, to their training on CBW, and this will assure that the medical providers themselves are aware of all the issues and are able to answer the questions of the service members.

Specifically with respect to pyridostigmine, pretreatment, as you know, for soman, I have directed that the information sheets which have been approved by the FDA be included in all of our training manuals.

Mr. Towns. Let me ask you this. I think I'm having trouble. Let me say what I really want to know. Does the FDA have the authority to prevent a DOD waiver request from going to the President? That's really what I want to know.

Mr. Raub. Yes, sir, it does. The way the interim rule is established, among other things, the FDA must determine that this investigational product is, in fact, at an appropriate stage to be used in that way, that there's a reasonable basis to expect it will be effective, and there is solid basis to expect that it will be safe. So if it doesn't meet what I'll call a test of maturity as an investigational product the FDA does not have a basis to make that determination.

Mr. Towns. Thank you very much.

Thank you very much, Mr. Chairman.

Mr. Shays. Thank you, Mr. Towns.

Dr. Bailey, how would you make sure recordkeeping and adverse reporting requirements are observed in the field?

Dr. Bailey. Fortunately, a great deal has happened since the lessons we learned in the Gulf war. We are now developing information systems that I think will provide us with the capability to do the kind of clinical tracking that I think we all know would be appropriate, including adverse reactions.

We have the next generation of the composite health care records, CHCS2, that up to a third of our organization will have in place by this coming summer. We also have for the battlefield the theater management information program which will assure us better tracking of situations, medical situations in theater. And we also recently have developed and are finally fielding the personal information carriers, which, as you may be aware--fortunately, that's not it, but, fortunately, this is.

You know that we've carried dog tags for years, and those dog tags, unfortunately, were notched so that they could be placed on the body of a service member that did not make it, and it didn't really provide much else except identification. This is the PIC, which is a Personal Information Carrier. This is the one that we have now chosen and are fielding, and as you can see it's about the size of a dog tag, in fact smaller.

And it would be interesting for you to see it sometimes, the information that is carried on here. There are about 16 megabytes--there are 16 megabytes on here. We can get off of

here not only dental records, not only the usual clinical information about adverse reactions, but we can put on here an MRI, CT scan, x rays, all of this on a PIC so that I think each member will be carrying this Personal Information Carrier with that medical data on it. And I think if you combine that with the theater management program and the involvement of our CHCS2 you're going to find better and better recordkeeping.

Mr. Shays. Thank you. The last question I would like to ask you is really a response to Michael Friedman regarding the--to the Food and Drug Administration dated October 29, 1997. It's from Dr. Edward Martin, Acting Assistant Secretary of Defense, and it also includes DOD comments on questions posed in the Federal Registry notice. And in regards to the issue dealing with medical treatment and medical research, does DOD consider the use of investigational products as force protection against chemical weapons and biological weapons as research or merely the off-label practice of medicine?

Dr. Bailey. I know the line in the letter you're referring to, and I know the weight that it carried. Yes, I believe as a physician that we are practicing the best medicine available to us to protect our troops.

Mr. Shays. So why apply for a waiver in that circumstance?

Dr. Bailey. I think, generally speaking, and I think one of my colleagues here may want to comment on this, but, generally speaking, as a physician, for instance, I am allowed to use a particular medication for a particular patient off label as a physician without going through a waiver of informed consent. However, I think that would be impractical when we're looking at thousands or hundreds of thousands of troops, besides which I think personally that would be inappropriate, and that in fact what this Executive order puts in place is the appropriate methodology for dealing with an investigational new drug.

Mr. Shays. Mr. Raub.

Mr. Raub. I'll add the point, Mr. Chairman, that, by its nature, when an investigational product is in clinical investigation, it simultaneously involves both patient care and research. In other areas, for example, the development and evaluation of new cancer drugs, we often say that the best available therapy many times is to be part of an experimental protocol. So we recognize all along that the physicians involved have the dual responsibility of their health care role and the question of research.

The vast majority of investigational new drugs are subject to those dual types of considerations. It's only this particular exception that is embodied in the Executive order and in the new FDA interim rule that contemplates the situation of an investigational drug far enough along for us to know a lot about it to be used, in effect, as a therapeutic or preventive intervention without informed consent because of the expected health benefits of that.

Mr. Shays. I guess what I'm trying to understand is the military--the DOD's attitude to off-label drugs and whether or not DOD is going to make the requests rare by not making the request because it's off label and, therefore, can still be used and not considered an investigational drug. I mean, that's one way to make it rare, is never ask but use it.

Dr. Bailey. If soman is not used on tomorrow's battlefield, we will not be asking for the waiver for PB.

Mr. Shays. Say that again.

Dr. Bailey. If soman were used, we would have no other option perhaps but to look for waiver of the informed consent.

I would hope that we would have enough intelligence provided to us to use any product, including the countermeasures we are discussing, ahead of time and to do that with informed consent, but the battlefield situation may not allow for that.

Mr. Shays. Be patient here. I just want to have some sense of, if DOD considers it medical treatment and not research, do they feel obligated to ask for waiver?

Dr. Bailey. Well, I think there are, again, several ways in which investigational new products are used, and I think you've heard them described here. They may be used in a research protocol. They may be used off label because they've been shown to be efficacious, because they're mature enough in the developmental process and moving toward full licensure.

I would just say that if it is an IND we will follow to the letter the rules set out in the Executive order and adhere to those rules and standards according to the FDA requirements and that does require perhaps in a military exigency a waiver of informed consent.

Mr. Shays. A lot of wiggle room here.

Dr. Raub, can you help me out here? I feel like this issue leaves such an open door. Is it possible that any off-label use of a drug can be used by DOD simply by the fact they deem it medical treatment?

Mr. Raub. Just as a bit of background first, Mr. Chairman, if I may. The notion of an off-label use by definition applies to a product that's already approved for something, so it will have gone through the normal FDA regulatory process first, especially for safety and for efficacy against some particular-----

Mr. Shays. But such as pyridostigmine bromide, that was off label, correct?

Mr. Raub. Yes.

Mr. Shays. OK. But they did ask for a waiver.

Mr. Raub. Correct.

Mr. Shays. But, under Dr. Bailey's response, I feel that she next time could say, no, we don't have to.

Mr. Raub. The second background point I wanted to make is that, under its normal practice, the FDA is not in the position of regulating the practice of medicine. Its oversight is limited to the sponsors of investigational products. And the medical community in general, as Dr. Bailey indicated, has the license to make off-label use in particular circumstances.

When it comes to an institutional policy I think some of our concerns arise that it is not just one-by-one physician decisions with individual patients but rather some policy, and we believe the Executive order and the new interim rule go a long way to regularizing how that would be done.

Mr. Shays. I just want to know as it relates to off-label use of drugs. I want to know how this Executive order specifically relates to off-label use of drugs. I am not saying it's not there. I just want to know the answer to the question. I'm really not getting an answer.

Mr. Raub. Again, the Executive order is focused on those instances where in a military operation the Department of Defense would be seeking the waiver of informed consent. So it is limited to that situation.

Mr. Shays. So the issue is that it is more than off label. How would this Executive order affect PB, for instance? Let's go back. How would it have affected it? Under Dr. Bailey's response, she would not have had to ask for informed consent. She would not have had to ask for a waiver.

Mr. Raub. I wasn't interpreting Dr. Bailey's response that way.

Dr. Bailey. Nor was it intended that way, Mr. Chairman. My intent was describing the various ways in which INDs are used, and I think that's what we have attempted to share with you. As a physician for a particular patient in a particular situation, I would be allowed to use a specific medication off label. I feel that is not clearly the situation in a broad policy effort as we would be making to protect our troops and their health protection in a military exigency. So I did not mean to imply that.

Mr. Shays. I can live with that answer. I'm going to put it in my words and tell me if it's accurate. Obviously, a physician is free to use an off-label use of a drug in any way they see fit, correct, if they believe it is dealing with a medical necessity. What I'm hearing you say, Dr. Bailey, is that if you decide to make the use of this drug universal for off-label purposes that you feel the obligation to ask for a waiver?

Dr. Bailey. To adhere to the IND requirements.

Mr. Shays. What is that?

Dr. Bailey. Or if it is not--if it is not needed, if the waiver is not needed but we are going to use investigational new drugs, that we adhere to all the standards for any IND, including informed consent of the individuals.

Mr. Shays. Let me back up. Technically, under your answer, you would not have to ask--have asked for a waiver on PB; is that correct?

Dr. Bailey. If I adhered to all the standards of an IND, yes, I could use PB as an investigational new drug if we went through all of the criteria for an IND, and we would do so.

Mr. Shays. Including getting informed consent?

Dr. Bailey. Yes.

Mr. Shays. I'm going to yield to my counsel.

Mr. Halloran. Who manufactures pyridostigmine bromide?

Dr. Bailey. It is a Roche product. Dufar, which is a Dutch company.

Mr. Halloran. And so, for purposes of FDA regulation, they're the regulated entity. How is it that DOD then would be conducting an IND or applying for an IND or for a use of someone else's drug?

Dr. Bailey. I would need to provide you an answer for the record on that.

Mr. Raub. May I just add, though, that is a common practice where someone other than the manufacturer of an agent may be the sponsor of an IND. Some of the agencies of our own department, for example, the National Cancer Institute, may on occasion be the holder of the IND application.

Mr. Halloran. What evidence or association between a manufacturer and the IND holder would FDA require?

Mr. Raub. Well, the FDA would require considerable information about, indeed, the involvement of the manufacturer, certainly the manufacturer's normal requirements for the purity of its products and all the other things are taken into account.

But in that situation I described, the other entity has the responsibility for the design and conduct of whatever proposed clinical studies are there, and many times that occurs when the manufacturer may not have its own commercial interests at high enough levels to pursue that development. But in the interest of the public such as, again, cancer drug development, an

agency of the government may choose to push that along. And in the same way the Department of Defense may be the holder of the IND because it sees the need for the particular military circumstance.

In the case of PB, I think we all agree that the most desirable outcome would be for the current IND work to continue, to come to fruition, and to have a sufficient basis for the FDA to be able to approve PB for the indication of protection against soman. That would obviate the need to exercise the Executive order for that circumstance.

Mr. Halloran. But would that approval then result in a change of the labelling that the manufacturer didn't ask for?

Mr. Raub. Yes, sir.

Mr. Halloran. It would.

Mr. Shays. Mr. Towns.

Mr. Towns. I just want to sort of clarify something here in my own mind. We're talking about investigational, and we're talk about the consent and all that, I understand that, and at the same time there's mandatory. Now, unless the military's changed, mandatory means that there is no consent. I mean, that happens, I mean, because after all you're in the military, and this is what the decision is, and you better follow it. So, I mean, am I correct on that? Because I think that's some of the problem here.

Dr. Bailey. If it's a lawful order and it is mandatory, yes, you would follow that. But I would again indicate our usage of tick-borne encephalitis. If we are not using--not looking for a waiver of informed consent but are going by the standards set for an IND, then we would in fact adhere to those standards and inform each service member about the product, and it would not necessarily be mandatory.

Mr. Towns. I am not quite clear what you mean. Run it past me one more time.

Dr. Bailey. If a vaccine--if we decide to give a vaccine, an order is given that you will take the vaccine, whether it's typhoid or malaria or anthrax, for instance, and it is an order, regardless of the status of the product, that is a line issue, and if it is a lawful order given to a service member, then it is a mandatory order regarding--regardless of the information that's given. That does not mean, however, that we do not try to provide, as in the case of pyridostigmine, all the possible information that we can to the service members.

Mr. Towns. And you do all that and I say no, what happens?

Dr. Bailey. Then you are subject to administrative and disciplinary action if it was a lawful order given and you are a member of the U.S. forces.

Mr. Towns. Thank you.

Mr. Shays. Just a few more questions here.

Dr. Raub, how will HHS ensure DOD is living up to the terms and the conditions of the waiver? And specifically I want to know what enforcement authority or sanctions does FDA or NAH have available in the event DOD fails to provide required individual information on investigational products or fails to maintain medical records?

Mr. Raub. First of all, Mr. Chairman, FDA has stepped up its collaboration with DOD and is trying to build the mechanisms where it will be able to get information after the waiver that will help it determine, for example, the patterns of adverse effects that may be seen and the like.

Second, the FDA rule requires the Secretary of Defense to apprise the President and the Commissioner of any circumstances



that might change, different from the intended use, that might require this being revisited. And, among other things, this could be the basis for the FDA withdrawing its certification under those circumstances.

Third, and I think most importantly, because this creates the framework through the President and involves, as Mr. Spotila indicated, not only the FDA but the expectation that DOD's own mechanisms of oversight will be there and the DOD Inspector General, we believe that the combination of that with FDA's expertise will go a long way to ensuring that the adherence after the waiver is consistent with the terms on which the waiver was based.

Mr. Shays. Bottom line, though, what basic authority or sanctions does FDA or NAH have? They can withdraw the waiver?

Mr. Raub. The FDA could recommend to the President that the waiver be withdrawn based on certain conditions that had occurred, yes, sir.

Mr. Shays. If DOD does not provide the information FDA wants, what can FDA do?

Mr. Raub. I think the first step FDA would take is working directly with the DOD to make very clear what information it wants and why and in what timeframe. I'd like to think that would be forthcoming; but if it weren't, I think the FDA would have an obligation through the Secretary of Health and Human Services to go to the President and indicate that the information needed to ensure a judgment of compliance needs to be in place. And we would look to the chief executive or the commander-in-chief to get that information.

Mr. Spotila. Mr. Chairman, I would add that we're aware that there is a need for implementation of this Executive order and that includes working out in more detail some of these procedures. OMB will be involved with FDA, with HHS and with DOD in trying to do that. We recognize there are more details that have to be worked out, but I would certainly reaffirm what Dr. Raub has said, which is that the President would want us to monitor the situation, and certainly if FDA indicated that we had this type of problem, we would respond quickly to it.

Mr. Shays. Who in OMB would monitor this? What unit within OMB?

Mr. Spotila. Well, it will be monitored in two respects. We have desk officers who actually work with each of these agencies who monitor and maintain lines of communication about their various programs. My office, the Office of Information and Regulatory Affairs, was instrumental in coordinating the interagency process that led to the development of the FDA rule, and so we have some involvement, but it is also true as the order directly states that the National Security Council and the Office of Science and Technology Policy will maintain some monitoring as well. So we have both OMB and these other executive office entities that will be involved in this.

Mr. Shays. Thank you.

Dr. Bailey, I'll just end with you. What obligations do you have to FDA?

Dr. Bailey. To provide--we are specifically charged within the Executive order to provide the training and the tracking and the information. But I think, as you have heard indicated here, we have a strong interagency working relationship to develop these protocols. They are under development now so that we can assure strict adherence to all the standards.

Mr. Shays. So I make the assumption that you recognize that DOD has an obligation to HHS to respond to their requests and

to live up to their obligations?

Dr. Bailey. Absolutely. Yes, sir.

Mr. Shays. Thank you.

Any other questions?

Thank you all very much, very helpful, very interesting.

Let me just actually conclude by allowing you all to make any closing comment you might want to make.

Mr. Spotila. No comment.

Mr. Raub. No comment, Mr. Chairman, other than thanking you for the opportunity to discuss these issues with you.

Mr. Shays. Thank you. They're important issues, and your testimony was helpful. Thank you.

At this time, we'll call our second panel, Dr. Arthur Caplan, director of the Center for Bioethics, University of Pennsylvania; and Dr. Charles McCarthy, senior research fellow, Kennedy Institute of Ethics, Georgetown University.

If you'd stay standing, please, Dr. Caplan, I'll swear you in.

[Witnesses sworn.]

Mr. Shays. Thank you.

For the record, both have responded in the affirmative. Dr. Caplan, you're first; and I appreciate both of you here.

Let me say that you have your written testimony. We are happy to have you read it, parts of it or all of it, but if you want to just respond in general, particularly since you've heard the first panel, that might be more helpful. So we'll roll with the punches, however you'd like to go.

OK, Dr. Caplan.

STATEMENTS OF ARTHUR CAPLAN, PH.D., DIRECTOR, CENTER FOR  
BIOETHICS, UNIVERSITY OF PENNSYLVANIA; AND CHARLES MCCARTHY,  
PH.D., SENIOR RESEARCH FELLOW, KENNEDY INSTITUTE OF ETHICS,  
GEORGETOWN UNIVERSITY

Mr. Caplan. OK. Well, I'm going to take the ``just respond'' for the interest of time.

Mr. Shays. Can you put the mic a little closer?

Mr. Caplan. I'm going to take the strategy of just responding with some brief comments, since the testimony is there, and thanks for opportunity to address the subcommittee.

Let me just respond on three areas.

First, the issue of would a request be rare or frequent and is there an adequate set of hurdles. I don't think the set of hurdles that's been created is adequate. I think there's some reason to think that requests could become very frequent.

We heard in the earlier panel some of the issues that have been dealt with with PB, with anthrax and tick-borne encephalitis, but in the world to come of biological warfare in particular, genetic engineering is going to open up the opportunity for a lot more rapid development of offensive weapons, and these are going to trigger attempts to find preventive responses, and I think we could be looking at a rapid series of requests to undertake preventive measures with relatively little information at hand on the part of the Department of Defense. And, to be blunt, I think without tough FDA requirements, tougher than have been put forward so far, the hurdles to get those requests in front of the President are not adequate. So I am concerned about the trigger issue.

The second thing I would say is I'm not convinced yet in the Executive order that there is adequate outside independent review of those requests by FDA or DOD. Charles comments on

this in his written testimony.

In situations where waivers are asked, emergency research, for example, where someone suddenly gets a heart attack and someone has a bright idea about how to treat them and they're not going to be able to consent, we ask for very tough IRB review, Institutional Review Board, or Human Experimentation Committee review, and I would like to see that provision toughened in the interaction between DOD and FDA for outside peer review, if you will, and community review.

The last thing I just wanted to comment on, Mr. Chairman, just in the interest of time, is what happens when consent is waived. And I think you know that I was a member of the Presidential Advisory's Committee on Veterans Gulf War Illnesses, and so I feel some obligation to comment here about what's in the record for what happens when waivers happen. Because things did not happen well from the Gulf war situation, and the track record for recordkeeping, followup and disclosure might generously be described, I think, as abominable.

What is laid out in the Executive order and in the backup Federal policy and rule so far I do not believe is adequate to ensure that if someone is given something without their permission they will be followed and tracked and adequately monitored to see what harm may have happened if an untoward event results from getting a vaccine or a drug or some other unapproved intervention. And I might humbly suggest that one way to make sure requests are rare and compliance is thorough is for some articulation of what a compensation policy might be if harm occurs. That hasn't been put on the table. That might be the best measure to ensure that requests are going to be infrequent to waive informed consent and that if they are granted that there's going to be serious tracking of what happens to people who don't get to give permission when something new is used.

I said that was my last comment, but I'll add one more just because it came up in the discussion. There is this ambivalence about is this research. Well, I don't doubt that people who gave PB weren't trying to do experiments in the field during the Gulf war, but the fact is that when you're using new experimental innovations you are then creating an experiment, and I think we have an obligation to our military members to carefully track and monitor what takes place, if only to learn what happened.

Mr. Chairman, 10 years after the PB was given out, we still don't know any more about it than we did 10 years ago. So not-- by not having adequate policy laid out, clear policy requiring public presentation of whatever the findings are concerning health impacts of situations where things are tried without informed consent, we can't learn, and so we find ourselves cycling around and around again trying to understand whether it's worth the risk to give out these unproven and sometimes inadequately tested interventions, not from malice, not from ill motives, from good motives, but, nonetheless, that's not the public policy that is going to get us where we want to go.

Mr. Shays. Thank you so much.

[The prepared statement of Mr. Caplan follows:]

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[GRAPHIC] [TIFF OMITTED] T4776.036

[GRAPHIC] [TIFF OMITTED] T4776.037

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[GRAPHIC] [TIFF OMITTED] T4776.044

[GRAPHIC] [TIFF OMITTED] T4776.045

[GRAPHIC] [TIFF OMITTED] T4776.046

Mr. Shays. Dr. McCarthy.

Mr. McCarthy. Mr. Chairman, I want to thank you and the committee for holding these hearings, and inviting us to testify. Addressing these issues at time when we are not in national crisis is of utmost importance, and I congratulate you for doing that.

You have a copy of my written testimony, and like Dr. Caplan, I see no reason to read most of that to you.

I served on the committee that was advising the FDA Commissioner back in 1990 when PB and BT were both under consideration and several other drugs that were subsequently dropped from the waiver request. I think the questions you asked the previous panel are still pertinent and answers are still somewhat murky, particularly the answers to your question concerning the off-label use of approved drugs. In fact, I think it would be very rare that we would not have an off-label use of drugs in a time of military crisis.

I consider the situation in which these drugs for toxins are used in warfare to be so different from the kind of use that would be made in a hospital or in a laboratory where workers are accidentally exposed to a toxic chemical or a pathogen. I think they are so different that in fact anytime you use an approved drug under the tensions of war with the possibility of bombs bursting, with personal suffering from lack of sleep, with the kind of situation the military are in, it is hardly what is conceived when a drug is carefully tested in a clinical trial where all of the variables in that trial are, so far as possible, carefully controlled.

I was partially reassured by the answers given, especially by Dr. Raub, but that part of the policy needs to be further clarified. We must consider that whether this drug is approved or not, when it is being used, in battlefield conditions it should be treated as an off-label situation. Consistent with FDA practice in all other kinds of off label situations, careful documentation of the effects of the use of that drug should be collected, and I think my recommendation is consistent with Dr. Caplan's.

In the intervening time since 1990 in the testing of drugs for civilian use, there has grown up a practice of trial surveillance by Data and Safety Monitoring Boards. We now have more than 10 years experience with such boards. Their functioning has been evolving what those boards are doing is tracking adverse events--not simply the number of adverse

events and the kind of adverse events--but adverse events on a case-by-case basis suffered by each subject of the drug trial. That's the kind of monitoring that I think is necessary.

Obviously, if you get a report from a military unit that there were 25 or 30 adverse events ranging from temporary rash to persistent headache, that doesn't tell you very much about whether those headaches or that rash were caused by the drug. It also doesn't allow you any followup with the individual. Because although you know that those adverse events occurred in that unit, you don't know which event applied to which military personnel. If adverse event data are to be meaningful, the adverse events have to be tracked by statisticians who relate each adverse event to an individual person. Then those who suffer a significant number of severe adverse events can be followed indefinitely or perhaps as long as they live. That way we can really find out how good or how bad these drugs are and whether they will be used in the future.

I think, furthermore, that the Data and Safety Monitoring Board [DSMB] would, in supplementing the work of the IRB that is already required, should be functioning in peacetime. The DSMB's ought to include about one-third military personnel, one-third civilian technical personnel, and one-third lay people, so that those boards represent the public. They should not be overwhelmed by military personnel, and both IRBs and DSMBs ought to be cleared for national security.

One of the difficulties that we had back in 1990 was that we had only the military telling us in very general terms, "we need approval of these drugs and we need them right away for the safety of our troops," the implication being that any denial of these drugs would somehow be sending our troops into battle without proper equipment. We had no way of independently evaluating that kind of information. For that reason I think these boards should be given security clearance to understand the risks, so far as they can be foreseen, that the military will be facing.

And, finally, I think there must be scrutiny either by the IRB, by the DSMBs or some other group to make certain that the training information is kept up to date. When the 1990 committee looked at the training information that was available on PB, we found that it was wildly inaccurate. Training manuals did not include the data that was known at the time. Consequently, military personnel who relied on the training data had bad information. There could have been no honest, informed consent because our troops didn't know the limitations of that drug, they did not know that it could not do all the things that were claimed for it in the military training manuals.

So far as I know, there has not been a linkage established between the training manuals which virtually every potential combatant uses and the information that is ever changing as we get more information and collect more data about these drugs.

That must be, now that we have computers and other much more rapid means of communication, it should be easy to keep data up to date within a matter of a week or two and personnel must be required to update their information so that they are and remain informed. Had I been a soldier in the Gulf war, basing my decisions on the training manuals, I would have felt that I was entirely immune to damage from chemical warfare or botulinum of various kinds, because the manuals overstated the effects of those drugs. Whereas, in fact, they can reduce those damaging effects, but they are far from a shield that totally

protects one against chemical or biological weapons.

That is the burden of my criticism. It is not that I think what has been proposed is not an improvement, and it is miles ahead of where we were in 1990. But still more needs to be done, and I think a lot of it can be done by clarification, communication and creation of DSMBs and by careful attention to the collection of data.

Thank you, Mr. Chairman.

[The prepared statement of Mr. McCarthy follows:]

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Mr. Shays. Thank you both very much.

This is not intended to cast aspersions on anyone, but I notice that Dr. Raub is here. I would like to thank you for staying.

Is there anyone from DOD or from the Office of Management and Budget that is here representing--not to speak but someone who will carry on that information we heard?

Thank you.

Which--DOD. Thank you for being here.

Anyone from OMB?

I am going to print up both your responses to your--both your comments as the transcript will be printed, and we are going to send it both to DOD and OMB, because I think that your comments are helpful and could make the Executive order more effective.

I will just comment, Dr. McCarthy, on your last point about if you were in the Persian Gulf. I think probably what I would have done is if I thought PB--a certain dosage would protect me at a certain level, I would have really blown it and taken twice as much.

Mr. McCarthy. That is another danger by the way.

Mr. Shays. I did that with my lawn this summer. I thought if a little fertilizer was good, I would use twice as much. I have a very dead lawn.

Mr. McCarthy. I have destroyed some lawns myself.

Mr. Shays. You have answered basically all the questions that I really intended to ask. I am just struck by some comments. It seems to me you need one monitoring board. It strikes me there needs to be some distance. I agreed with all four of your points, Dr. Caplan. It makes me want to write a letter to both OMB and to DOD to make some suggestions.

Dr. Raub, I would love to invite you not in a way to have a debate but just to respond to what you heard, because I have really no questions I want to ask. If you don't mind, I do know you were here and were paying attention.

Mr. McCarthy. Parenthetically there, I would like to say there was a time when Dr. Raub was my immediate supervisor. I have great respect for his opinions, and I don't expect that we are going to end up disagreeing very much.

Mr. Shays. Does that mean that you just feel an obligation

to agree with him?

Mr. McCarthy. No. And he knows that even when I was his subordinate I did not always agree with him.

Mr. Caplan. Mr. Chairman, I feel an obligation to clarify one thing that came up in the previous panel, and it does relate to the issues of informed consent and off label, which were hard to follow and were confusing.

It is true doctors can use drugs off label. It is never true they can do so without the informed consent of the patient. It is true they have discretion to try out all things. You are not immunized from getting informed consent. When we are talking at the policy level about going off label for PB or tomorrow's next generation of vaccines against something, there will be off-label uses, doctors have discretion to use them, but you would still require a waiver of informed consent to do so. So you are not privileged to do whatever you want, as long as you can take something off label.

Mr. Shays. But let me just make sure I am clear on the terminology now. You have to inform them, or they can, without a waiver, object to taking the drug?

Mr. Caplan. Absolutely, can still object to taking the drug without that waiver. You could object. So the presumption is you absolutely have the discretion as an individual doctor to go off label, but you are supposed to get the consent of your patient sometime.

Mr. Shays. Then it seems to me then the answer of DOD would have been a simple one.

Mr. Caplan. Correct.

Mr. Shays. That scares the hell out of me.

Mr. Caplan. Correct.

Mr. Shays. I wish I had known that information with the previous panel.

Dr. Raub.

Mr. Raub. Thank you, Mr. Chairman. I realize in staying I ran the risk of coming back to the table, but----

Mr. Shays. You know what? Let me say this. I go out of my way to be very courteous the second time around, because I do appreciate your being here.

Mr. Raub. I understand that from prior hearings as well, Mr. Chairman. I did stay because of the importance of the issues and my high regard for my two colleagues, here, and I wanted to hear what they had to say.

The interim rule as published by the FDA also includes a comment period, and it includes a comment period for the very purpose of getting this kind of analysis and commentary about it.

In my judgment, I continue to believe that the hurdles are indeed formidable to get any product through, to get this waiver, and I also believe the Commissioner of Food and Drug and her staff have done a superb job in putting this interim rule together.

That said, I don't think they believe they are in sole possession of revealed truth. This comment period is serious, and we will take seriously comments such as these and from other members of the public as we seek to get this right.

Mr. Shays. Thank you. That is very comforting. Thank you very much.

Dr. Caplan, do you have any other things, words of wisdom, that you want to make sure you put on the record like the last one? Dr. McCarthy.

Mr. McCarthy. I think--as I indicated before, I think there

needs to be appointed in every military unit that is likely to receive drugs of this kind, there needs to be a person there with responsibility, clear responsibility, for collecting the data and reporting it to a DSMB.

That person who collects also needs to be thoroughly familiar with everything that is known about the drug at the time that it is being administered, so that there will be good information in training manuals or other issuances by the DOD and perhaps FDA in conjunction with DOD, there will be someone at the scene to answer questions and explain to military personnel who are trained and accustomed to obeying orders without much question. We need to go an extra mile in educating troops with the latest and best information about both the strengths and the limitations of our information about the proposed drug.

A major training event or training effort needs to accompany each of these products. The whole structure including IRBs, DSMBs, and data collection needs to be set up in a time of peace. Because I know from my 1990 experience that it was virtually impossible to add new structures and responsibilities when we were morally certain that was would start within a matter of weeks. No such training program could be initiated in that kind of timeframe.

Mr. Shays. Do any of you know--Dr. Caplan, maybe in your work with the President's commission--know what drugs were actually requested and not given informed consent, I mean not given a waiver?

Mr. Caplan. None that I know of.

Mr. Shays. We were led to believe there were some.

Mr. McCarthy. My recollection was, at least in the initial request, an off-label use for Valium was included, and there was another substance, the name of which I have long since forgotten, that was a skin cream to help prevent skin burns from various kinds of chemicals that might have been used or included in weapons.

When FDA looked into the skin cream, it found out that there was very little quality control in the manufacture of it, and it didn't work very well even for ordinary sunburn. The DOD withdrew that one.

I don't recall what happened or why Valium was withdrawn. I think it was because there was great concern if each soldier had a large packet of Valium in his pack and an attack was imminent, that many soldiers might take Valium and might be quite passive in the face of the enemy.

So I believe those were the reasons, but I am relying on memory and some anecdotes, and that may or may not be accurate.

Mr. Shays. We will note that. Very interesting.

Mr. Caplan. I was just going to make two other comments, brief ones.

One is, it does seem to me that, in trying to understand the question of followup and harm that may happen and tracking it, it is important to emphasize one other thing which did come up in the Advisory Committee on Gulf War Illnesses and I am not sure has been prepared, and that is the importance of having a good sample of soldiers, military personnel, reservists as well as active, with good health physicals before deployment. In other words, it is very hard without a baseline to figure out what happened later.

And I am not persuaded, and I have tried to stay on top of this from a distance now, that the pre-deployment health monitoring of the military, both Reserve and Active, a sample



of them, not everyone, but it is enough to give us that baseline. So when we talked about what happened and if we get a waiver and what are the side effects and so on, we need to have that baseline in place. And that has to be something that I hope FDA would think about.

The other point I would make is in the world to come, not a pleasant one for biological warfare, I think there may be many reasons why we choose not to say what it is we have, antidotes or preventive things, we are thinking about to the other side, because that world I think is going to be in flux pretty fast in terms of genetically engineered anthrax or genetically engineered other viruses and bacteria that are nasty and tough to lay in stockpiles of things. We may not want to say much publicly. That leads to reasons that informed consent might not be sought that have nothing to do with risk-benefit but had to do with national security.

In those circumstances, I hope that FDA takes seriously the need it is going to have to carefully assess that request before agents are deployed more than consultatively. It is going to have to make a hard call, and I hope they have the administrative authority to do it.

I think my prediction, Mr. Chairman, would be in a world to come we are going to be playing a sort of roulette with what we have got and what the other side has, and requests could get pretty frequent, and the only stopping point for those requests is going to be behind the door at FDA consideration, what the evidence looks like. It may be the skin cream sort of thing that Charles is talking about, or it may be something useful. But you are going to need the authority to do that, and I am not quite convinced yet that that is laid out in the way the Executive order and the proposed final rule are laid out.

Mr. Shays. This is really fascinating.

Dr. McCarthy, any other comment you want to make?

Dr. Raub.

Mr. Raub. No, sir.

Mr. McCarthy. I just want to thank the committee for giving us this opportunity.

Mr. Shays. Let me just ask one other last area, and you triggered it, and I am not trying to prolong this hearing, but I just want to know if it is something I should be thinking more about, and that is with nuclear weapons and a missile delivery system, there was the debate about a missile defense system, and basically we allowed the Russians, the Soviet Union, to protect Moscow and we were allowed to protect a certain area, but there was the general view if we started to protect they would start to protect, and then there would be almost a willingness potentially to use the weapon thinking you could protect yourself.

So what you said, Dr. Caplan, is triggering this emotion. If, for instance, an adversary believes they have protected their force against certain chemicals or biological agents, would they be somewhat inclined to then use them and does that--is the best protection, potentially, not doing the Russian roulette, literally saying if you use this weapon, then we will use all of the force necessary, even nuclear, to respond to weapons of mass destruction, rather than trying to have a prophylactic in one area or another and try to guess where that is going to be? Is this an issue policymakers are having a significant dialog about?

Mr. Caplan. I don't think sufficiently. Because I think we are stuck in thinking, unfortunately, about the array of

primitive biological weapons out there, the anthrax, which in some sense is more interesting as a terrorist weapon than it is to put on a battlefield. If you are trying to win a battle, you don't want someone keeling over from anthrax 30 days later. You want them dead relatively quickly, I would assume. So chemical weapons look more interesting. Biological have different impacts.

I think, again, looking at the genomapping project, looking at what is out there for the ability to do targeted attacks on people with particular genotypes, this is coming. The kind of policy question you are asking about for dealing with both military situations and terrorist situations, for approval for preventive agents, it is going to take some rethinking of our policies about how we want to deal with that.

Just having the old stocks of the old disease entities and the old stocks of the old chemical weapons, well, it is the 21st century. We are about to be able to change those fast, and we may need to have both treaties and agreements about how this is going to play out and also keep something in our hip pocket about how we are going to respond if somebody is foolish enough to launch this kind of thing.

So I would say, yes.

Mr. Shays. I think the biggest deterrent to Saddam Hussein using chemical weapons was he knew that Iraq would be annihilated.

Mr. Caplan. Yes. I think that kind of thinking is going to be important for us to continue to engage in about what our defense posture is going to be in the face of these things. Because if you can change a virus, say, smallpox, into something nastier, or anthrax, relatively quickly, and make it something you can't protect against under any circumstances, or targeted to particular sub-groups of a population, you are into an era of warfare we haven't thought through as a matter of political policy.

Mr. Shays. I have concluded my questions.

Dr. Raub, I again appreciate your making the point that this is an interim rule and you are listening and so are others. I appreciate that a lot.

Do you have any other comment you would like to make?

Mr. Raub. No, sir.

Mr. Shays. Dr. McCarthy, are you all set?

Mr. McCarthy. Yes, I am all set.

I would like to simply comment and say, for the very reasons that you intimated and Dr. Caplan emphasized, I think the people who are reviewing these things need to have security clearance so that they can make those kinds of balancing recommendations about should we be developing these kinds of defenses, are they likely to escalate or call for new kinds of attacks because we can now defend against this one, so it invites our opponents to develop another.

I think that is a balancing kind of judgment, and I don't think it can be done by those who do not have security clearance to understand the best intelligence we have and to wield those judgments carefully. That is why, even though I would like to see a number of civilians on these committees, I think they have to have clearance. Otherwise, they are flying blind.

Mr. Shays. I totally agree with that. I agree with most of the other comments made by this panel. Thank you very much.

We will conclude this hearing. Thank you.

[Whereupon, at 12 noon, the subcommittee was adjourned.]

