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

HEARING

BEFORE THE

SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS, AND INTERNATIONAL RELATIONS

OF THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

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

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 informa-

tion 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:]

Statement of Rep. Christopher Shays

November 9, 1999

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 these 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.

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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 need 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.

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

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 Presi-

dent 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:]

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

STATEMENT OF
THE HONORABLE JOHN T. SPOTILA
ADMINISTRATOR
OFFICE OF INFORMATION AND REGULATORY AFFAIRS
OFFICE OF MANAGEMENT AND BUDGET
BEFORE
THE SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS
AND INTERNATIONAL RELATIONS
OF THE COMMITTEE ON GOVERNMENT REFORM
U.S. HOUSE OF REPRESENTATIVES

November 9, 1999

Good Morning, Chairman Shays and members of the subcommittee. Thank you for inviting me here today to discuss the President's Executive Order 13139 which was signed on September 30, 1999. Titled "Improving Health Protection of Military Personnel Participating in Particular Military Operations," it represents a thoughtful effort to implement the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (the "Act"). It creates new procedures that will act as health safeguards.

Before discussing the Order in more detail, let me first summarize the events leading to its issuance.

Background

Prior to the Persian Gulf War, the Department of Defense (DOD) concluded that Iraq had weaponized certain 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 Food and Drug Administration (FDA) for that specific use. DOD discussed with FDA its belief that the use of specific investigational drugs might provide important protection to military personnel serving in the Gulf region. After a formal request from DOD in October 1990, FDA published an interim final rule in December of that year allowing the Commissioner to waive FDA's existing requirement to obtain informed consent from such personnel if doing so was not feasible in certain military exigencies. While this was a significant change in practice, the previous Administration believed that we should recognize exceptions to such standard practice when necessary to ensure the best health protection for our Armed Forces during certain military operations.

For the Gulf War, FDA granted DOD waivers for the use of two investigational products – pyridostigmine bromide (PB), a drug considered potentially useful as pretreatment against certain nerve gases, and botulinum toxoid, a vaccine to protect against botulism. My understanding is that DOD only implemented the waiver for PB.

In evaluating the use of this waiver of informed consent during the Gulf War, we have learned many lessons. The Presidential Advisory Committee on Gulf War Veterans Illnesses specifically recommended that the FDA regulation on waiver of informed consent be reviewed. In July 1997 FDA sought public comment on whether its rule permitting waiver of informed consent in certain military exigencies 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 continue to have a mechanism to request waivers of informed consent, although a modified one. Section 1107 of the 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 (1) not feasible; (2) contrary to the best interests of the military member; or (3) not in the interests of national security. This statute gave us a framework for development of an Order and the new, accompanying FDA rule.

After reviewing the results of an interagency process coordinated by OMB, the President signed Executive Order 13139 on September 30, 1999. Consistent with section 1107 of the Act, the Order establishes the process that DOD must follow to seek a waiver of informed consent. The Order establishes new procedures for the consideration of a waiver request, and is supplemented by a companion interim final rule, published by FDA on October 5, 1999, establishing the standards and criteria that the President will apply in making the waiver determination. Both reflect a consensus reached by all of the relevant agencies on the best means of implementing the Act.

The Order and the FDA rule strike an appropriate balance between the need to protect individual rights and the need to provide the best health protection for our military troops. They are the product of a careful and deliberative process. Together, they significantly improve the safeguards available to protect our military personnel in the future.

Our policy will continue 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 rare circumstances, however, protection of our deployed military personnel may require use of an investigational drug (a drug not yet approved by FDA for a specific use). 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 contingency 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.

My testimony today focuses on the requirements prescribed by the Order. HHS will describe FDA's interim final regulations and DOD will discuss how it plans to implement the new requirements.

Executive Order 13139

Executive Order 13139, "Improving Health Protection of Military Personnel Participating in Particular Military Operations", represents a significant departure from the previous waiver approval process. It (1) establishes a process for waiver decisions to be carefully evaluated in a timely manner and used only when absolutely necessary; (2) creates multiple layers of oversight to ensure accountability and that necessary safeguards for military troops are met; and (3) 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.

Process for Waiver Determinations

Before administering an investigational drug to members of the Armed Forces, DOD must obtain informed consent from each individual unless the Secretary of Defense can justify to the President a need for a waiver of informed consent. Under the Order, only the Secretary of Defense can request a waiver. As mentioned earlier, the Act permits the President to waive the informed consent requirement for the administration of an investigational drug to a member of the Armed Forces during a particular military operation under three conditions: When obtaining consent (1) is not feasible; (2) is contrary to the best interests of the member; or (3) is not in the interests of national security. As prescribed by the Act, the President will apply the standards and criteria set forth in FDA's regulations in making a determination under the first two conditions. To narrow the use of a waiver under the Act's third option and to provide maximum protection for our troops, the Order reflects the President's decision to also consider FDA's standards and criteria in deciding on waivers based solely on national security grounds.

At a minimum, the Secretary of Defense's waiver request must contain: a full description of the threat, a statement that certifies and a written justification that documents that the Secretary has complied with each of FDA's standards and criteria, and any additional pertinent information, including the minutes of the Institutional Review Board's (IRB) deliberations and the IRB members' voting record.

To ensure that FDA is brought into the decisionmaking process early, the Secretary of Defense must develop the waiver request in consultation with FDA. Once the waiver request is complete, the Secretary must submit the waiver request to the President and provide a copy to the FDA Commissioner. The Commissioner must expeditiously review the waiver request and certify to the Assistant to the President for National Security Affairs (APNSA) and the Assistant to the President for Science and Technology (APST) whether FDA's standards and criteria have been adequately addressed and whether the investigational new drug protocol should proceed. The Commissioner will base the decision on a complete assessment of the criteria specified in the rule, including FDA's own analysis of the safety and efficacy of the investigational drug in relation to the medical risk that could be encountered (a risk-benefit calculation).

The Order directs the President's top national security and science advisors to carefully review the waiver request, along with the Commissioner's certification and recommendation, and to 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 and will provide written notification to the Secretary of Defense and the Commissioner.

Multiple Layers of Oversight

The process established in the Order creates multiple layers of oversight to ensure accountability and compliance from DOD. Before a waiver request can be made, an Institutional Review Board (whose role has been specifically strengthened for this purpose) must review DOD's protocols for military use of investigational drugs. In addition, there are numerous checks built into the waiver approval process: a waiver request can only be made by the Secretary of Defense; a strong and clearly-defined role is established for the FDA; and the request is reviewed by the President's top national security and science advisors, who provide him with an advisory opinion on whether he should grant a waiver.

If a waiver request is granted, the Order requires the DOD offices implementing the waiver, DOD's Inspector General, and the FDA to conduct ongoing review and monitoring to assess whether DOD continues to meet the standards and criteria. DOD also 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 requires the Secretary to notify the Congressional defense committees and the public that a waiver has been granted.

Enhanced Safeguards

The Order builds in additional procedures and safeguards to protect the health and well-being of our military troops prior to, during, and subsequent to the use of a waiver in certain military exigencies. For example, the Order requires DOD to provide ongoing 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. This training will be incorporated into ongoing chemical and biological warfare defense training, as appropriate, and will include information about the Act and the FDA regulations. DOD will describe these activities in greater detail.

In addition, in the event that DOD requests a waiver, DOD must submit its training and health risk communication plans to FDA and the reviewing IRB. The information communicated to military personnel affected by the waiver must include: (1) the basis for the President's determination; (2) the means for tracking the use and adverse effects of the investigational drug; (3) the benefits and risks of using the drug; and (4) a statement that the investigational drug is not approved (or not approved for the intended use). 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 one year, or an alternative time not to exceed one year, as specified by the President at the time of approval. 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.

Conclusion

We hope that DOD will not need to invoke the waiver procedure at all in the future. If they do fine it necessary, however, we believe that the Order, combined with FDA's new interim final rule will significantly improve the safeguards necessary to protect the health of our military personnel. They implement the Act faithfully and also represent a consensus of the relevant agencies throughout the Administration.

In closing, we note that the Order charges DOD to collect intelligence on potential health threats that may be encountered in an area of operations, and to work with HHS to ensure that appropriate countermeasures are developed. DOD and HHS are to study these potential products through scientifically-based research and development protocols to determine whether each product is safe and effective for its intended use. Both Departments have firmly 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 increasing health safeguards for 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. 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:]

RECORD VERSION

Use of Investigational New Drugs for Force Health Protection

STATEMENT BY

Dr. Sue Bailey
Assistant Secretary of Defense for Health Affairs

Submitted To

SUBCOMMITTEE ON NATIONAL SECURITY,
VETERANS AFFAIRS AND INTERNATIONAL RELATIONS
COMMITTEE ON GOVERNMENT REFORM

FIRST SESSION, 106TH CONGRESS

November 9, 1999

NOT FOR PUBLICATION
UNTIL RELEASED BY THE
SUBCOMMITTEE ON NATIONAL SECURITY,
VETERANS AFFAIRS AND INTERNATIONAL RELATIONS

Chairman Shays and Distinguished Committee Members, I am honored to appear before your Committee today to address the use of investigational new drugs for force health protection. I am Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs. At your request, our testimony will specifically address federal policies governing the administration of investigational new drugs (IND) to U.S. military personnel.

The United States today faces the monumental challenge of establishing a credible medical defense against chemical and biological weapons in contexts of both military operations and civilian terrorist response. Our forces also face endemic environmental health threats as they deploy around the world. For some of these threats, there are not yet available, FDA approved prevention or treatment products. -Some treatment products, which show clinical promise, are in a state of development en route to possible licensure. Government agencies must work together to provide access to products that can make a life or death difference to that servicemember on the battlefield. Our goal is to provide our military personnel with products that will protect them while deployed on a particular operation and will not adversely affect their long-term health. The Executive Order and FDA rules we are discussing today show the Administration is prepared to meet that goal.

On September 30, 1999,President Clinton signed Executive Order 13139, entitled "Improving Health Protection of Military Personnel Participating in Particular Military Operations." This Executive Order addresses the President's role under 10 U.S.C. 1107, a law that authorizes a Presidential waiver of informed consent for the use of investigational new drugs for force health protection in certain military operations.

Section 1107 reflects a Congressional recognition that when an investigational product is the only means available to protect against a lethal chemical/ biological weapon or endemic health threat, the lives of individual members, the safety of their comrades who rely on them, and the success of the military mission may require uniform use of the medical protection. Further, the nation would demand that military commanders do all in their power and authority to employ prudent medical countermeasures in the face of lethal health threats. The consequences of an action which leads to foregoing availability of a needed investigational new drug will lead to an unacceptable military operational setting in which the lives of personnel and the accomplishment of mission are jeopardized. But section 1107 also strikes a careful balance. Cognizant that use of investigational products generally requires informed consent under FDA rules, section 1107 states that informed consent will always be done through specific notice requirements; and may only be waived by the President. This careful balance is also incorporated into the Executive Order, which makes clear that: "Waivers of informed consent will be granted only when absolutely necessary."

Supporting the E.O. is a new regulation issued by the FDA on October 5, 1999, the interim final rule. Also based on 10 U.S.C. 1107, this rule establishes the standards and criteria both the President and the Secretary of Defense will use to consider the potential need to use an investigational new drug for force protection in a particular military operation without the informed consent of the affected military personnel. These standards and criteria are very detailed and exacting.

The next important action in establishing policy for the use of investigational new drugs for force health protection will be the issuance by the Secretary of Defense of a DoD Directive incorporating the requirements of 10 U.S.C. 1107, the Executive Order, and the FDA interim final rule. Following involvement of multiple DoD components affected, I expect this to be issued early next year.

I would like to summarize the key elements of DoD policy that I believe will be incorporated into the Directive.

1. Force health protection. It is DoD policy that personnel carrying out military operations will be provided the best possible force health protection, including safe and effective medical countermeasures to chemical, biological or radiological warfare and endemic disease threats. The DoD will make every effort to utilize products approved by the FDA when available to provide the needed medical countermeasure. When no FDA-approved product is available to meet a foreseeable threat, DoD will carry out appropriate research and development program activities directed toward obtaining general commercial marketing approval by the FDA of safe and effective medical countermeasures. In limited circumstances in which at the time of the need for a force health protection countermeasure against a particular threat no safe and effective FDA-approved drug or biological product is available, DoD components may request approval of the Secretary of Defense to use an IND if justified based on the available evidence of the safety and efficacy of the drug and the nature and degree of the threat to personnel.

2. Approval by the Secretary of Defense to use INDs. Use of an IND for force health protection requires approval of the Secretary of Defense. A Commander of a Combatant Command will submit a request through the Chairman of the Joint Chiefs of Staff (CJCS). Such a request must document a confirmed, high threat for which the use of an IND is needed, consideration of the risks and benefits of use of the IND, and compliance with all applicable requirements. DoD will develop a specific treatment protocol for use of the IND. The protocol will comply with FDA regulations and be approved by a duly constituted Institutional Review Board under FDA rules, prior to submission to the FDA for review. In most of these cases, the IND would be administered on a voluntary basis.

3. Requests by the Secretary of Defense to the President for a waiver of informed consent. If the protocol suggests a waiver of informed consent, numerous other requirements become applicable. Under 10 U.S.C. 1107, only the President may grant a waiver of informed consent to use an IND for force health protection and only the Secretary of Defense may request that the President grant such a waiver. Under the law, the President may grant a waiver only upon a determination that obtaining informed consent: 1) is not feasible; 2) are contrary to the best interests of the member; or 3) are not in the interests of national security.

4. Standards and criteria for a waiver of informed consent. In making a determination that informed consent is not feasible or is contrary to the best interests of the member, the President and the Secretary shall apply the standards and criteria in the FDA interim final rule. In making a determination that informed consent is not in the interests of national security, the Executive Order states that the President will consider those standards and criteria. Those standards and criteria are the following:

(1) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(2) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(3) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(4) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(5) A duly constituted institutional review board (IRB) established and operated in accordance with special FDA rules has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent.

(6) The risks and benefits of using the IND are evaluated with consideration of: the context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional; the nature of the disease or condition for which the preventive or therapeutic treatment is intended; and to the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(7) Applicable logistical record keeping systems are capable of tracking and will be used to track movement of the IND from supplier to the individual recipient.

(8) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by section 1107) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(9) Medical records of members involved in the military operation will accurately document the receipt by members of the written information.

(10) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations.

(11) The protocol will provide for adequate follow-up to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(12) While preparing to use an IND, DoD is also pursuing drug development, including a time line, and marketing approval, in accordance with FDA regulations, with due diligence.

(13) The FDA has concluded that the IND protocol may proceed subject to a decision by the President on the informed consent waiver request.

(14) Applicable DOD components will provide training to the appropriate medical personnel and potential recipients on the specific IND to be administered prior to its use.

(15) The Commander of the Combatant Command has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(16) DoD components will report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period for which the waiver is needed) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(17) DoD will provide public notice of the decision.

(18) Use of the investigational drug without informed consent otherwise conforms with applicable law.

5. Institutional Review Board approval. An Institutional Review Board (IRB), compliant with FDA rules, will approve every protocol for the use of an IND for a particular military operation. In any case in which a protocol proposes to include a waiver of informed consent, the board must include at least three non-affiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB). Detailed minutes of the meeting(s) at which the proposed protocol was discussed shall be provided to the Secretary of Defense and the FDA. The Board must review and approve: the information sheet to be given to military personnel; the adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product; the adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and an informed consent form as required by FDA regulations in those circumstances in which the protocol includes informed consent by some or all personnel involved.

6. Content of request by the Secretary of Defense to the President. A request by the Secretary to the President for a waiver of informed consent shall be developed in consultation with the FDA. Upon submission by the Secretary of the waiver request to the President, a copy of the request shall be provided to the Commissioner of FDA. The content of the request shall at a minimum include a full description of the threat, including the potential for exposure. If the threat is a chemical, biological, or radiological weapon, the waiver request shall contain an analysis of the probability that weapon will be used, the method or methods of delivery, and the likely magnitude of its affect on the exposed individuals. The request will also include documentation of compliance with the requirements of the FDA standards and criteria. If the request is based on the statutory grounds that informed consent is not feasible or contrary to the best interests of the member, the documentation will include a statement that certifies and a written justification that documents that each of the criteria and standards has been met. If the Secretary finds it highly impracticable to certify that all such criteria and standards have been fully met because doing so would significantly impair DoD's ability to carry out the particular military mission, the Secretary will provide to the President a written justification that documents which criteria and standards have or have not been met, explains the reasons for not meeting those which have not been met, and provides additional justification why a waiver should be granted solely on the grounds of national security. The submission will also include any additional information pertinent to the Secretary's determination, including the minutes of the IRB meetings at which the IND use was considered. In this later case, the President would only be able to grant a waiver on the ground of national security.

7. Action required after waiver of informed consent. Following a waiver of informed consent by the President, DoD components shall ensure proper implementation. DoD components responsible for implementation shall conduct an ongoing review and monitoring to assess adherence to the standards and criteria, and adhere to any periodic reporting requirements specified by the President at the time of the waiver approval. The Secretary shall provide to the President any required reports, with a copy to the FDA Commissioner. The DoD Inspector General will also conduct an ongoing review and monitoring to assess adherence to the standards and criteria. In addition, the Secretary will, as soon as practicable, make the congressional notifications required by section 1107, as well as public notification through a notice in the Federal Register. Further, the Secretary will notify the President and the FDA Commissioner if the threat countered by the IND changes significantly or if significant new information on the IND is received. A waiver expires at the end of one year (or an alternative time not to exceed one year specified by the President) or upon notification by the Secretary to the President that the particular military operation creating the need for the use of the IND has ended, whichever is earlier. A request by the Secretary for a renewal by the President of a waiver must meet the same criteria as the original request and shall include any new information available relevant to the issue.

8. Training and risk communication. Under section 1107, and consistent with the E.O. and FDA's regulation, when using an IND for force health protection, DoD will provide prior notice to personnel receiving the drug or biological product: that it is an IND (including specific information on whether it is approved by FDA and/or whether it is unapproved for its applied use); the reasons the IND is being used; information regarding the possible side effects of the IND, including any known side effects possible as a result of interaction of the IND with other drugs or treatments being administered to such personnel; and any other information as required to be disclosed by the FDA as a condition of acceptance of the IND protocol. Furthermore, DoD will ensure that health care providers who administer the IND or who are likely to treat members who receive the IND receive the IND information. DoD components shall ensure that medical records of personnel who receive an IND accurately document the receipt of the IND and the required notice. In addition to these actions concerning specific INDs, DoD will also provide ongoing 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, during chemical and biological warfare defense training and other training, as appropriate. This ongoing training and health risk communication shall include general information about section 1107, the Executive Order, and the FDA regulations. Moreover, there are special additional training and health risk communication requirements when informed consent is waived. If the President grants a waiver of informed consent, DoD will provide training to all military personnel conducting the waiver protocol and health risk communication to all military personnel receiving the specific investigational drug to be administered prior to its use. The Secretary will submit the training and health risk communication plans as part of the investigational new drug protocol submission to the FDA and the reviewing Institutional Review Board. Training and health risk communication in informed consent waiver cases will include at a minimum: the basis for any determination by the President that informed consent is not or may not be feasible; the means for tracking use and adverse

effects of the investigational drug; the benefits and risks of using the investigational drug; and a statement that the investigational drug is not approved (or not approved for the intended use). DoD components will keep operational commanders informed of the overall requirements of successful protocol execution and their role, with the support of medical personnel, in ensuring successful execution of the protocol.

I want to again stress that it is our desire to only use drugs that have been approved and licensed to protect against specific health threats our military members might face. It is DOD's intention to work with the FDA to conduct carefully controlled research that will lead to development and approval of those licensed products. To facilitate that development, the Food and Drug Administration on October 5, 1999, issued a proposed rule to establish a mechanism for approving drugs and biological products for use against lethal or permanently disabling toxic substances when efficacy studies in humans ethically cannot be conducted. This rule would establish standards for using well-controlled animal trials when the results of those animal studies establish that the drug or biological product is reasonably likely to predict clinical benefit in humans. This method of demonstrating effectiveness of a product would be subject to a number of pre-approval and post-approval restrictions to assure its prudent use. DoD believes this is a very important step toward making available safe and effective medical countermeasures against chemical and biological weapons in both the military and civilian terrorism contexts. The Department of Defense is committed to seeking licensure of all of the products it is developing, and this new rule will offer a significant boost to allow us to meet this commitment.

These new actions by the Congress in enacting section 1107, the President in issuing Executive Order 13139, the FDA in issuing its proposed and interim final rules, and the Defense Department in developing implementation plans have together formed a new approach, conceived by lessons learned in the recent past and a recognition of threats we face in the near future. We must have effective force health protection for our soldiers, sailors, airmen, and marines. Education of our commanders, our health care professionals, and all of our service men and women must be the cornerstone of a risk communication strategy. Whenever possible, we need to avoid reliance on investigational new drugs to protect our forces. When that is the only protection we have, we need to use INDs with an exquisitely careful balancing of risks and benefits. Although our desire is to be able to offer informed consent in all cases, there may be rare circumstances that is not possible. In that event, we will still ensure that compliance is founded on understanding the nature of the risk and the benefit of the medical protection. The Department of Defense is committed to effective implementation of this policy.

Thank you again for the opportunity to testify.

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 need-

ed 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:]

Mr. Chairman and Members of the Committee, I am Dr. William Raub, Deputy Assistant Secretary for Science Policy at the Department of Health and Human Services (DHHS). I am pleased to be here today to discuss Federal policies governing the administration of investigational new drugs to U.S. military personnel, including the safeguards and protections recently announced in the Executive Order 13139 issued by the President and the interim rule on waiver of informed consent issued by the Food and Drug Administration (FDA or the Agency). The issuance of these documents represents a long, cooperative, interagency effort aimed at providing the best protection possible for military personnel needing investigational drugs during particular military operations.

DHHS was a party to this cooperative effort and believes that the resulting criteria take into account the protection of individual military personnel while accommodating the national security interests that arise during the conduct of military operations. Protection of individuals receiving health care services, including those receiving investigational new drugs, is an issue of paramount concern to DHHS. This stance is reflected in the positions taken by DHHS concerning the Patient Bill of Rights, medical data privacy, the allocation of human organs for transplantation and many other issues involving the provision of medical care to individuals. This is particularly appropriate in the use of investigational products. There may not be any FDA approved medical products to treat or prevent certain diseases or conditions. The lack of approved products becomes particularly critical in the context of military operations when investigational products may constitute the best treatment for a particular disease or exposure to a chemical or biological warfare agent. DHHS believes, however, that exceptions from informed

consent should apply rarely and only when sufficient additional protections are provided to the military personnel affected. We believe that the new interim rule and the Executive Order provide those protections.

ESTABLISHMENT OF NEW STANDARDS AND CRITERIA UNDER THE 1999 INTERIM RULE

On October 5, 1999, FDA published in the Federal Register a new interim rule that contains new strengthened criteria and standards the President can use in making informed consent waiver determinations. Among other things, the interim rule requires that each member involved in the military operation be given, prior to the administration of the investigational new drug, a specific written information sheet providing full information on the product. It also requires the Department of Defense (DOD) to provide, consistent with classification requirements, public notice in the Federal Register describing the waiver of informed consent determination, a summary of the most updated scientific information on the products used, as well as other pertinent information. The interim rule also requires DOD to provide training to the appropriate medical personnel, and potential recipients, on the specific investigational new drug to be administered prior to its use.

The President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation if it is determined that obtaining consent is not feasible, is contrary to the best interests of the military member, or is not in

the interests of national security. If a determination is based on the grounds that it is infeasible or contrary to the best interests of the military member, the President must apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements. Executive Order 13139 also specifies that the President will consider the standards and criteria even under grounds of national security. This new interim rule contains those standards and criteria.

The interim rule requires the Secretary of Defense to certify and document to the President that the standards and criteria in the interim rule have been met. Section 50.23(d)(1)(i) through (d)(1)(iv) contains the fundamental information necessary to make an informed assessment of risks and benefits within the context of the specific military situation. Under these paragraphs, the Secretary of Defense must certify and document that:

(1) the extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an investigational new drug application (IND);

(2) the military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness;

(3) there is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug; and

(4) conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and threaten the accomplishment of the military mission.

In order to help ensure that the President is provided all relevant information related to the effects of the investigational drug, the rule requires the Secretary of Defense to certify and document in his or her request for a waiver determination that DOD has explained:

(1) the context in which the investigational drug will be administered;

(2) the nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(3) to the extent it is available, information on conditions that could alter the effects of the investigational drug (21 CFR 50.23(d)(1)(vi)).

In order to improve record-keeping over that which occurred during the Gulf War, the Secretary of Defense is required to document and certify that DOD's record-keeping system is capable of tracking, and will be used to track, the proposed treatment from the supplier to the individual recipient; and, that medical records of members involved in the military operation will accurately document the receipt by members of the notification required by Section 50.23(d)(1)(viii) as well as any investigational new drugs in accordance with FDA regulations (21 CFR 50.23(d)(1)(vii), (d)(1)(ix), and (d)(1)(x)).

As noted earlier, the rule requires the Secretary of Defense to document and certify that each member involved in the military operation will be given, prior to the administration of the investigational new drug, a written information sheet describing the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product (21 CFR 50.23(d)(1)(viii)). In addition, the information sheet is required to contain the following: (1) Clear notice that the drug being administered is an investigational new drug or a drug unapproved for its applied use; (2) the reasons why the investigational new drug or drug unapproved for its applied use is being administered; (3) information regarding the possible side effects of the investigational new drug or drug unapproved for its applied use, and (4) such other information that, as a condition of authorizing the use of the investigational new drug or drug unapproved for its applied use, the Secretary of Health and Human Services may require to be disclosed. FDA intends to review the information sheet as part of its review of the use of the investigational product under an IND in order to determine its adequacy.

The Secretary of Defense must document and certify that DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use (21 CFR 50.23(d)(1)(xiv)). DOD must also document and certify that DOD will provide adequate follow-up to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product (21 CFR 50.23(d)(1)(xi)).

The requirements for Institutional Review Board (IRB) review of protocols for military use of investigational drugs without informed consent have been strengthened and further specified beyond those required for conventional INDs. The provisions of the interim rule include the following:

- The duly constituted IRB is to be responsible for reviewing the study. It must review and approve the investigational new drug protocol and the administration of the investigational new drug without informed consent as a prerequisite for the study to proceed (21 CFR 50.23(d)(1)(v)).
- DOD's request for a waiver must include the documentation of minutes of IRB meetings at which the protocol was reviewed (21 CFR 56.115(a)(2)).
- The IRB must include at least three nonaffiliated members who are not employees or officers of the Federal Government (other than for purposes of membership on the IRB) Section 50.23(d)(2).
- The IRB must review and approve the contents of the required written information sheet on the investigational product; the adequacy of the plan to disseminate information; the adequacy of the information and the plans for its dissemination to health care providers; and an informed consent form in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved (Section 50.23(d)(3)).

The rule provides for FDA to complete its review of the investigational new drug protocol and conclude that it may proceed subject to a decision by the President on the informed consent waiver request (Section 50.23(d)(1)(xiii)). FDA will provide a written

notification to DOD after it has completed its review, either granting permission for the protocol to proceed subject to the President's decision on the informed consent waiver request or, if appropriate, placing the study on clinical hold.

The rule contains two provisions to help ensure that informed consent waiver determinations continue to meet the standards and criteria of this rule after an initial waiver has been granted by the President. Section 50.23(d)(1)(xv) requires the Secretary of Defense to certify and document that DOD has stated and justified the time period for which the waiver is needed, not to exceed one year. For a waiver to exceed one year, this paragraph requires such a waiver to be separately renewed under the standards and criteria contained in 21 CFR 50.23(d). Section 50.23(d)(1)(xvi) places a continuing obligation on DOD to report to FDA and to the President any changed circumstances relating to these standards and criteria or that otherwise might affect the determination to use an investigational new drug without informed consent.

To encourage public access to information about products for which an informed consent waiver is granted, Section 50.23(d)(1)(xvii) requires DOD to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

Finally, in order to help ensure that DOD adheres to applicable statutes and laws, Section 50.23(d)(1)(xviii) requires the Secretary of Defense to document and certify that the use of the investigational drug without informed consent otherwise conforms with applicable law. Section 50.23(d)(5) states that "[n]othing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations."

As noted above, DHHS believes that exceptions to the informed consent requirement should be made rarely and in narrow circumstances and that it is preferable to establish the safety and efficacy of products before their general use in large populations. The new rule, 21 CFR 50.23(d)(1)(xii), therefore requires the Secretary of Defense to certify and document that it is pursuing drug development and marketing approval for the investigational drug with due diligence.

ANTECEDENTS TO THE EXECUTIVE ORDER AND INTERIM RULE

As noted above, the interim rule was the result of much effort and took into account the interests of all affected parties. It is important to understand the background of the rule and the actions leading up to its promulgation.

The use of investigational drugs is regulated by provisions of the Food, Drug and Cosmetic (FD&C) Act. In order for clinical testing to proceed with unapproved products, an IND application must be filed with FDA. The IND must contain information sufficient to demonstrate that it is reasonable to study the drug in humans, including

information on drug composition, manufacturing and control data, the results of animal studies and, if available, prior human testing, and the protocol for the planned study. More importantly, the investigator must agree to a number of commitments designed to protect the rights and safety of human research subjects, including obtaining written informed consent from subjects, obtaining approval of an IRB before proceeding, and reporting to the sponsor of the study adverse effects that occur in research subjects. An IRB is a board or committee that reviews, approves and provides continuing oversight of biomedical research involving human subjects to ensure the right and welfare of the human subjects. (21 CFR Part 56).

Under the FD&C Act, sponsors must require investigators to certify that they will inform subjects receiving drugs under an IND that the drugs are investigational and "obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgment, contrary to the best interests of such human beings" (21 USC § 505). There have been few instances in which obtaining informed consent has not been considered feasible or contrary to patients' interests.

There are three limited exceptions to FDA's informed consent requirements. These exceptions are: 1) for a physician to preserve the life of an individual patient; 2) for the conduct of a narrow class of research in emergency settings; and 3) for use by DOD of specific investigational products in military operations. FDA regulations governing all three of these informed consent exceptions are primarily focused on protecting the rights and safety of patients. The third exception to our informed consent requirements, the use

of an investigational drug or biologic in certain situations related to military exigencies is the focus of this hearing.

During the months preceding the Persian Gulf War, DOD had discussions with FDA regarding the potential use of specific investigational products in military personnel serving in the Gulf region. It was thought that the products discussed represented the best preventive or therapeutic treatment for diseases endemic to the area and in providing protection against the possible use of chemical or biological weapons.

Thus, in response to DOD's request, FDA published in the December 21, 1990, Federal Register (55 FR 52813) an interim regulation amending its informed consent regulations at 21 CFR 50.23(d). The interim regulation allowed Commissioner of Food and Drugs to determine, upon receipt of an appropriate request from DOD, that obtaining informed consent from military personnel for use of a specific investigational drug or biologic would not be feasible in certain circumstances, and to grant a waiver from the requirement for obtaining such consent.

On December 28, 1990, DOD submitted protocols under INDs and requests for waiver of informed consent for pyridostigmine bromide 30-milligram (mg) tablets and the botulinum toxoid vaccine. Pyridostigmine bromide was considered a potentially useful pretreatment against certain nerve gases; the botulinum toxoid vaccine is widely accepted as offering potential protection against toxins produced by Clostridium botulinum, the bacterium that causes botulism. The Commissioner approved DOD's waiver requests for

pyridostigmine bromide 30-mg tablets and botulinum toxoid vaccine on December 31, 1990, and January 8, 1991, respectively. Both products were administered to portions of the military personnel who participated in Operation Desert Storm. Following the cessation of combat activities, the DOD notified the Commissioner in a letter dated March 15, 1991, that DOD considered the two waivers granted under the interim rule to be no longer in effect. DOD also informed the Commissioner that DOD had ultimately decided to administer the botulinum toxoid vaccine on a voluntary basis.

There has been extensive examination of the use of the 1990 interim rule during the Persian Gulf War. The Presidential Advisory Committee on Gulf War Veterans' Illnesses' final report reviewed these issues in detail. In its' interim report (February 1996), the committee described a number of shortcomings in DOD's use of investigational products during the Gulf War and recommended, among other things, that FDA should issue a Notice of Proposed Rulemaking to revisit the adequacy of disclosure to service personnel; adequacy of record-keeping; long term follow-up of individuals who receive investigational products; and additional procedures to enhance understanding, oversight, and accountability. The report further suggested that FDA should explore possible alternatives to the 1990 interim final rule, such as an approval standard that recognizes surrogate endpoints and other data indicative of efficacy for vaccines, drugs, devices, and antibiotics to protect against chemical and biological warfare agents.

DOD's experience during the Gulf War with pyridostigmine bromide and the botulinum toxoid vaccine was described in detail in the request for comments on the 1990 interim rule. Concurrent with the request for comments on the interim rule, FDA was also evaluating DOD's experience in implementing INDs, as well as waivers under the interim rule during the Gulf War, in order to obtain specific factual information and to assess DOD's compliance with FDA requirements. In the ongoing evaluation of the use of investigational products in the Persian Gulf, significant deviations were identified from Federal regulations. These deviations were set forth in July 22, 1997, and December 2, 1997, letters from FDA to DOD.

Experience with the use of the waiver provision of the 1990 interim rule suggests two conclusions: (1) To the extent possible, military personnel should receive treatments whose safety and effectiveness have been fully evaluated; (2) where it is necessary to utilize investigational agents and to waive informed consent, new standards and criteria for doing so should be developed that will better ensure protection of the troops receiving the investigational product.

In the July 31, 1997, Federal Register (62 FR 40996), FDA published a "Request for Comments" that discussed the use of investigational drugs and biologicals in military and other emergency settings to treat or prevent toxicity of chemical or biological substances. The public comments received on the 1990 interim rule pointed out significant areas that needed to be strengthened, including: provision of adequate information about an investigational product before its use; adequate follow-up to assess whether there are

adverse health consequences that result from the use of the investigational product; adequate oversight, accountability, and record-keeping when investigational agents are used; and involvement of non-DOD personnel in decisions to use investigational products without informed consent. All of these areas have been addressed in the new interim rule that establishes the criteria and standards for the President to use in making an informed consent waiver determination.

The new interim rule also necessitates a change to the regulations for human drugs so that those regulations are consistent with this rule. In the interim rule, 21 CFR 312.42 is amended to explicitly state that an investigation may be placed on clinical hold pending a determination by the President to waive the prior consent requirement for the administration of an investigational new drug. If FDA invokes this reason for a clinical hold, it will mean that review of the protocol is completed and FDA has concluded that the study may proceed; however, subjects may not be enrolled in the study until a positive decision on the informed consent waiver request has been made by the President and FDA has provided written notification to DOD that the clinical hold has been removed.

Section 731 of the Defense Authorization Act

Public Law 105-261, the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (Defense Authorization Act) answers the controversial question of whether waiver of informed consent in military operations is ever appropriate. In passing this legislation, Congress has concluded that the President may waive the informed consent

requirement for military personnel engaged in a particular military operation in certain situations. The President is established as the sole authority for making such a waiver of informed consent determination. FDA will be involved in this process through its traditional role of reviewing specific protocols under its investigational new drug regulations. The Commissioner of Food and Drugs will also play a key role in reviewing the waiver of informed consent request to the President.

Section 731 of the Defense Authorization Act, amending 10 U.S.C. 1107(f), became effective on October 17, 1998. Under new 10 U.S.C. 1107(f), the Commissioner of Food and Drugs no longer has the authority to issue a waiver of informed consent with respect to military operations. Section 1107(f)(1) of Title 10 provides for the President to grant such a waiver in the case of the administration of an investigational new drug or drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation.

Section 1107(f)(1) of Title 10 authorizes the President to waive informed consent if the President finds that obtaining informed consent is: (1) not feasible; (2) contrary to the best interests of the member; or (3) not in the interests of national security. The first two grounds (lack of feasibility or contrary to the best interests of recipients) are specified in Section 505(i) of the FD&C Act (21 U.S.C. 355(i)). Section 1107(f)(2) provides that, in making a determination to waive informed consent on the grounds that it is not feasible or contrary to the best interests of the armed services member, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of

the prior consent requirement on that ground. Because Section 1107(f)(1) of Title 10 refers to waiver of informed consent in connection with military operations, the relevant FDA regulations referenced in Section 1107(f)(2) of Title 10 would be any regulations dealing with waivers in this context.

Executive Order 13139

FDA's October 5, 1999, interim rulemaking coincided with the publication of Executive Order 13139, entitled "Improving Health Protection of Military Personnel Participating in Particular Military Operations" and implementing Section 1107 of Title 10.

The Executive Order explicitly states the expectation that the United States Government will administer products approved for their intended use by FDA. In the event that the Secretary of Defense considers an investigational product to represent the most appropriate countermeasure for diseases endemic to the area of operations or to protect against possible chemical, biological, or radiological weapons, the product may, under certain circumstances and strict controls, be administered to provide potential protection for the health and well-being of deployed military personnel in order to ensure the success of the military operation.

Under the Executive Order, the Secretary of Defense shall develop the waiver request in consultation with FDA. The Commissioner of FDA shall expeditiously review the waiver request and certify whether the standards and criteria of the relevant regulations have been adequately addressed and whether the investigational new drug protocol may

proceed subject to a decision by the President on the informed consent waiver request. FDA shall base its decision on, and the certification shall include an analysis describing, the extent and strength of the evidence on the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation. Finally the Executive Order establishes FDA review of training and health risk communications plans.

FUTURE USE OF FDA-REGULATED PRODUCTS BY DOD

There are important ways that FDA can contribute to DOD's mandate to protect military personnel that are consistent with FDA's mission and regulations and also mesh with DHHS's initiatives on bioterrorism and commitment to human subject protection. FDA's existing mechanisms for providing access to investigational products under an IND will continue to be available to any entity that complies with the Agency's specified requirements. Both DOD and FDA recognize, however, that some of the IND requirements may not be feasible in certain military situations. Based on the lessons from use of investigational agents during the Gulf War, DHHS believes that DOD's needs can best be met through DOD's support of drug development efforts leading to approval of products found to be safe and effective. We share DOD's goal of getting the best products to military personnel. Thus, we are committed to working with DOD to resolve the safety and effectiveness questions that may allow FDA to approve the drug and biological products for use in military operations and during military exigencies.

In order to provide pharmaceutical agents that are safe and effective in protecting military personnel, FDA believes that DOD must focus its efforts on drug development. Under existing regulations FDA can expedite access to new drugs by accelerating approval (subpart H of 21 CFR part 314 and subpart E of 21 CFR part 601). In addition, consistent with the recent changes to the FD&C Act on fast track products made in the Food and Drug Administration Modernization Act of 1997 (FDAMA), FDA is committed to facilitating development and expediting the review of drugs for serious and life-threatening conditions that address unmet needs (§ 506, FDAMA (21 U.S.C. 356)).

Moreover, FDA has proposed an additional mechanism for product approval that relates to the evidence needed to demonstrate safety and efficacy for drug and biological products for use against lethal or toxic substances when efficacy studies in humans cannot ethically be conducted. FDA is proposing to amend its new drug and biological product regulations to identify the information needed to provide substantial evidence of the efficacy of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This proposal would apply when the traditional efficacy studies in humans are not feasible and cannot be ethically conducted under FDA's regulations for adequate and well-controlled studies in humans. We recognize the need for adequate medical responses to protect or treat individuals exposed to these lethal or permanently disabling toxic substances.

In these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions could be approved for marketing based

on evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans (21 CFR 314.126). Under the proposed rule, FDA could rely on the evidence from animal studies where:

(1) There is a reasonably well understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product;

(2) the effect is independently substantiated in multiple animal species, including species expected to react with a response predictive for humans;

(3) the animal study endpoint is clearly related to the desired benefit in humans, generally, the enhancement of survival or prevention of major morbidity; and;

(4) the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans, and it is therefore reasonable to expect the effect of the product in animals to be a reliable indicator of its efficacy in humans.

In order to minimize the need to use investigational products during military exigencies, FDA has been working with DOD in its drug development efforts related to these products. DOD has agreed to identify those products that may provide protection to military members, develop appropriate drug development plans for each product, and establish a timeframe for completion.

CONCLUSION

Mr. Chairman, we hope the information presented here is useful to the Committee in examining the difficult issues surrounding the use of investigational drug products by the armed forces. DHHS has learned an enormous amount through our 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. Thank you.

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 going 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, diptheria, 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, Institu-

tional 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:]

Testimony to the Subcommittee on National Security, Veterans Affairs and International Relations, of the House of Representatives of the Congress of the United States

November 9, 1999

Arthur L. Caplan, Ph.D
Trustee Professor
University of Pennsylvania
and
Director of the Center for Bioethics
University of Pennsylvania Medical Center

Thank you for the opportunity to address the Subcommittee. I am honored to have the opportunity to do so. In offering testimony today I will be drawing upon three areas of expertise and experience that I have which bear on the question of the adequacy of existing Federal policy governing the use of investigational drugs and vaccines for military personnel.

I have been actively involved in shaping Federal policy governing human experimentation ethics most recently having chaired a blue-ribbon committee at the University of Pennsylvania which issued a consensus paper on the need to overhaul existing human subjects protections.

I also serve as the Chair of Advisory Committee to the Department of Health and Human Services, Centers for Disease Control and Food and Drug Administration on Blood Safety and Availability. This position has allowed me to understand some of the issues raised in vaccine development and what may soon be possible with respect to the genetic engineering of biological weapons.

Lastly, and most importantly, I will draw upon what I learned serving as a member of the Presidential Advisory Committee on Gulf War Veterans' Illnesses. During my service on that committee I came to understand the devastating impact that illnesses associated with service during this conflict have had on the lives of so many Americans. I also came to understand the importance of addressing a question that this nation has never adequately grappled with—what constitutes appropriate medical innovation and experimentation with respect to individuals who are engaged in the service of their country?

Protecting Human Subjects: Problems with Informed Consent and Peer Review

In recent years there has been a failure in the reliability of the existing system of human subjects protections to adequately protect the rights and welfare of those involved as subjects. Especially troubling is the fact that some of those who have not been adequately protected are persons who cannot for various reasons look out for their own interests. Recent scandals involving research with children, persons with mental illness, persons with mental retardation, homeless persons, the institutionalized elderly and others who are vulnerable due to impairments of or an absence of competency

make plain the importance of having an adequate set of ethical and legal safeguards for those who serve in the role of human subjects.

In raising questions about what is appropriate Federal policy for using unapproved drugs, new vaccines or any other innovative medical procedure I believe it is important to acknowledge that the current system of protections we have in place for human subjects in medical research is not adequate. We rely on two protections for persons involved in medical research. One is the right to give full informed consent prior to any involvement in clinical research. The other protection is to provide independent peer review of all research involving human subjects by means of what are commonly referred to as human experimentation committees but whose formal name is institutional review boards or IRBs. Important questions have been raised about the adequacy of both protections in today's high stakes and high-pressure research environment. Some of the concerns about informed consent and IRB review as adequate to protect subjects are very relevant in thinking about the adequacy of Federal policy with respect to innovative uses of drugs or vaccines for military personnel.

Since the days of Nuremberg, it has been widely understood by biomedical researchers that consent to involvement in human experimentation is an inviolate moral rule. At the same time it has also been widely understood that there are persons who for a variety of reasons cannot provide informed consent. In such circumstances, special provisions have been made to allow others to act as surrogates who can act in the best interest of the incompetent or impaired individuals.

But, it is not always clear when a particular innovation constitutes medical research. A doctor who wants to try a new device, or surgical procedure or drug in desperate circumstances may not always have created a research protocol for doing so. In some instances it is not clear what actually constitutes medical research as opposed to simple innovation since the definition of research that is used relies on the intent of the researcher to create generalizable knowledge. And when gray zone cases of research are encountered, while all agree that informed consent is necessary as a matter of ethics, there is no agreement or what needs to be said or who should give consent if the potential subject is not capable of doing so.

There is no doubt in my mind that, while it is often hard to define what constitutes medical research, the presumption should be that when doubt exists the default assumption should be that what is new is research. If this position is correct then it is especially important that persons involved with new or experimental or innovative drugs and devices are given every opportunity to consent to their use.

Equally importantly, if informed consent is going to serve as an adequate protection for human subjects then it must be carefully secured. In practical terms this means that individuals must be given full and complete information, have some time to reflect on the risks and benefits of participation in medical experimentation, understand that they may choose not to do so without penalty and know what compensation is available to them if untoward results should occur.

Unfortunately, Federal policy has never clearly articulated that the right to informed consent should be extended as far as possible to military personnel. During the Gulf War inadequate efforts were made to secure informed consent from those who were treated with unproven anti-biological and anti-chemical warfare agents.

Our Advisory Committee on Gulf War Veterans' Illnesses found that two investigational products, pyridostigmine bromide (PB) and botulinum toxoid (BT) vaccine were used without the informed consent of our troops. The Food and Drug Administration allowed consent to be waived by issues an Interim Final Rule. The argument made at the time was that the reality of military operations did not permit informed consent to be obtained.

I am worried that we are growing increasingly lax as a matter of public policy with respect to insisting that informed consent must be obtained when innovation or research is undertaken. Filling out forms and producing signatures on pieces of paper are not examples of informed consent. A subject who understands what is going on, knows the risks and understands the options is informed consent.

Too often the excuse is made that time or circumstance does not permit obtaining informed consent. But even for active military personnel informed consent is less an obstacle then it might appear. Of course it is impossible to obtain consent in the context of combat. But when troops are to be deployed it is often possible to obtain their consent without interfering with military

efficiency or revealing information that would be of value to this nation's enemies. I fear that the executive order issued by the President on September 30, 1999 does not make it absolutely clear that the burden of proof in seeking a waiver or an exemption to informed consent must rest totally upon those who seek the waiver. Nor do I think the FDA is given a sufficiently active role in making a determination of whether consent must be waived.

The legacy of distrust that flowed in the wake of complaints about illness and disability suffered by veterans of the Gulf War has a lesson to teach. Soldiers as much as any other American should have the right to consent to innovation, experimentation or research with drugs, vaccines, or any other medical intervention. Only in the most extraordinary circumstances and with the highest level of review possible should exceptions be made to that principle.

There are situations in civilian life where the principle of informed consent to research by the subject has been waived. In emergency circumstances where a patient is suddenly and unexpectedly rendered ill and incompetent we have allowed some research to be done without the consent of the

subject. But in these extraordinary circumstances the policy that has emerged requires extraordinary scrutiny and peer review as well as general notification to the community that research may be going on and that they may not be able to consent.

In the executive order that the President issued there is not the same level of independent peer review as exists with respect to research under emergency circumstances. Again, the order and the policy are inadequate because there is no call for special IRB oversight, documentation of decision-making to permit a waiver. It is understandable that situations may arise in which it would be imprudent or impossible to gain informed consent for the use of investigational or experimental interventions with military personnel. But, such circumstances require the highest level of scrutiny and deliberation and, ultimately, accountability none of which are present in current Federal policy.

What Must Be Done When Consent is Waived

It is especially important when consent is in fact waived that obligations to those facing risks that they cannot consent to be honored. This was not done

in the Gulf War. The Presidential Advisory Committee on which I served found that those soldiers who were given PB and BT did not receive adequate notification after the fact, that record keeping about who got what was basically abominable and that no systematic long-term follow up was conducted to examine the health effects of these investigational substances. Indeed, we know not much more today about the health effects of PB and BT then we did ten years ago as a result of inadequate follow up.

The President's executive order of September 30, 1999 while commendable for calling for tracking use and effects of any investigational drug for which consent has been waived does not go far enough. Federal policy must have strict and explicit guidelines about the prompt notification of persons after the fact as to what they have been exposed to, detailed guidance about the kind of follow-up that is required of those so exposed and some clear policy about what will happen if adverse effects do occur. To expose persons without consent to unproven medical interventions requires that our society makes every effort to insure that should something go wrong the soldiers that have been exposed know that fact, that a useful sample of such persons is intensively monitored for health and illness for a reasonable duration of

time and that a compensation policy is in place for them if they are indeed hurt or injured.

Is It Really Research Anyway?

Some might argue that all the talk of informed consent and the rights of human subjects that have followed in the wake of decisions to use PB and BT in the Gulf and more recently to inoculate our troops against anthrax misses the point. The goal of the use of investigational interventions with military personnel is to protect them against harm and to insure their effectiveness and readiness to accomplish their missions.

In one sense this is true. It is somewhat of a strain to talk about a soldier facing attack by biological weapons as a human subject when a new vaccine is given or to look at efforts to insure combat readiness by means of a mass vaccination of troops with the best available agents. But in another sense it is very misguided to battle over whether or not the concept of research or experimentation applies.

The goal of the military is to successfully accomplish the missions and tasks it is given. Sometimes this requires great sacrifice on the part of military personnel including the grim realities of disability and death. But, these facts should not muddy the reality that in the effort to get the mission done it is still important not to treat soldiers with any less dignity or respect then they otherwise would enjoy as civilians regarding their medical care.

While those giving out the PB or the anthrax vaccine or the next generation of anti-biological and chemical warfare drugs may have no interest in conducting medical experiments the fact remains that what is new and untested when it is used creates an experimental situation. It is vital that everything possible that can be learned from such a situation be learned. We did not do that in the Gulf War. The President's Executive order as it now stands does not insure that we will do it in any future conflict. And that would be a terrible mistake in that it will lead soldiers to distrust their doctors and their government while at the same time slowing the progress that must be made in finding out what is safe and effective in the new era of warfare that we are entering.

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-labele 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 eveloving 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 as individual person. Then those who suffer a significant number of severe adverse events an 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 manuels 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 combatants 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:]

TESTIMONY

before

THE HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT AFFAIRS

SUBCOMMITTEE ON NATIONAL SECURITY,
VETERAN'S AFFAIRS,
AND INTERNATIONAL RELATIONS

Christopher Shays, Connecticut
Chairman

Presented by
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November 9, 1999

Mr. Chairman and distinguished members of the Committee, I consider it an honor to be invited to testify before you this morning concerning a set of issues that will affect the protection of the rights of personnel in our military services and may affect their health and well being. First, let me introduce myself. My name is Charles McCarthy. I am a Senior Research Fellow at the Kennedy Institute of Ethics at Georgetown University. For fourteen years, prior to 1992, I served as the Director of the Office for Protection from Research Risks (OPRR) at the National Institutes of Health (NIH). In that capacity, I negotiated -- with the Department of Defense (DoD) and fifteen other departments and agencies of the federal government -- the Common Rule for the Protection of Human Subjects involved in Biomedical and Behavioral Research. The Common Rule was promulgated in June of 1991. In the Fall of 1990 I was invited by the Commissioner of Food and Drugs to serve on a committee that would make recommendations to the Commissioner and to the Secretary, Health and Human Services (HHS), concerning a request from the Department of Defense for a waiver of informed consent for the administration of pyridostigmine bromide (PB) and botulinum toxoid (BT) vaccine to military personnel who were thought to be at risk of exposure to chemical or biological weapons in the Gulf War that -- although it had not begun -- seemed inevitable. Several other drugs were included in the initial DoD request for waiver, but -- after some negotiations -- the list was narrowed to these two compounds.

I must confess to you that my descriptions of past events are based on my recollections. The events that I describe are therefore anecdotal. They are not documented because I retained no records or notes of this experience after I left the government. There could be unintended errors in my account.

My testimony will address the following points:
I. A brief summary of certain ethical rules regarding participation in research by military personnel.
II. A description of the climate that prevailed and the arguments used when decisions were made concerning the DoD request on the eve of the Gulf War and lessons to be learned from that experience.
III. A discussion of the safeguards now in place. And recommendations for additional safeguards.

I. ETHICAL RULES REGARDING PARTICIPATION IN RESEARCH BY MILITARY PERSONNEL.

The personnel of our military services are required to surrender many rights that are guaranteed to civilian citizens of our country. Military personnel are required to live in places not of their own choosing, often separated from their families and friends. They are required to follow orders to function in ways they would not otherwise choose. In some cases they are required to follow

orders they consider unwise, although they are not required to follow orders that require them to carry out unlawful acts. They are expected to place the safety and well-being of their military units above their own safety and well-being. They are required, if so ordered, to place themselves in harm's way, that is, to risk their health and even their lives, to protect national interests. Because they have surrendered many of their freedoms, our civilian population is able to enjoy freedom from coercion in virtually all activities. For these reasons, military personnel deserve the gratitude and respect of the entire country.

Nevertheless, military personnel do not surrender all of their rights. We have a long standing tradition in this country, supported by ethics scholars, that military personnel, no less than their civilian counterparts, ***are not required to and must not be ordered to participate in biomedical or behavioral research***.

The reasons why military personnel are not, as a general rule, required to participate in biomedical or behavioral research are not difficult to understand. The purpose and very essence of research is to seek answers to questions. If the outcome of research could be predicted, it would not be research. Since the outcome of research cannot be predicted, it makes no sense to require that military personnel who make so many other sacrifices participate in activities that may not help their military units, and may not contribute to the protection or furtherance of national interests.

Furthermore, research on the effects of drugs or biologics under battlefield conditions cannot be tested prospectively, (1) because the risks of exposing subjects to biological or chemical weapons outweigh any possible benefits that might come from the research; and, (2) because research investigators cannot know, but can only estimate, the kinds of weapons that a military leader like Sadam Hussein might employ against allied military personnel. No research could be devised that would provide evidence that PB and PT would be safe and effective in the Gulf war that was soon to take place.

In extremely rare instances of national need, the rights of military personnel ***not to participate*** in research may be abridged. The conditions of national need are not well worked out. However, in general it is thought that if the research ***is the only way*** to have a chance of reducing casualties among military units functioning in defense of the well-being of citizens of this country, then military personnel may be involved in research without their informed consent.

II. THE DECISION MAKING CLIMATE SHORTLY BEFORE THE GULF WAR

In 1990, the FDA conceded that classifying PB and BT as "investigational drugs" was partially misleading. These compounds had been used -- on an investigational basis -- with partial success to treat laboratory workers exposed to toxic chemicals and pathogens. FDA believed that it had evidence to show that the effect of the drugs on human beings was understood and predictable under carefully controlled conditions. The evidence was limited because the number of cases of

exposure had not been great, and because the toxins and pathogens to which workers had been exposed were clearly identified. No long term adverse events had been associated with the use of these compounds.

It was then argued that because the classification of "investigational" was not fully merited, approval of the use of the drugs in military personnel was analogous to the use of an approved drug for an unapproved purpose.

During this period the media, following the lead of President Bush, tended to demonize Sadam Hussein. Sadam was, and still is to a large degree, presented to us as the greatest threat to world stability since Adolph Hitler. He was reputed to be prepared to use a large and sophisticated arsenal of chemical and biological weapons that had been tested in the Iran-Iraq war. Speculation suggested that his decision to invade Kuwait and his defiance the United Nations, especially the United States, was based on his confidence that UN troops could not defend themselves against Iraq's internationally outlawed weapons. Few questioned the assertion that he intended to utilize these weapons. Military personnel suggested to the FDA committee that failure to use the drugs at hand would -- in effect -- be sending allied troops into battle without proper equipment.

After a number of meetings of the FDA committee, it was recommended that ingestion of PB and PT could be required for military personnel thought to be in danger of chemical or biological weapons. The argument that prevailed in the FDA committee, as I recall the meetings, was that the military use of these drugs was analogous to an unapproved use of an approved drug. In this line of reasoning, the troops were more like patients receiving a drug that was demonstrated to be in their best interests rather than serving as research subjects for testing the safety and efficacy of a drug of unknown consequences. .

Several conditions were attached to the committee recommendation. The first was that each recipient should be identified and followed, and that adverse reaction data should be carefully collected from each individual who received the drugs. Collection of data was judged to be equivalent to Phase IV data collected in relation to marketed drugs. The second condition was that the drugs should be used exclusively in personnel who faced a high probability of exposure to chemical or biological weapons. The third was that military handbooks used for training personnel should be revised because they wildly overstated the effectiveness of the drugs, failed to indicate that they had not been tested under battle conditions, and identified few if any risks associated with the use of the drugs. So far as I am able to judge from the reports that have circulated subsequent to the Gulf War, none of those conditions was met.

III. SAFEGUARDS NOW IN PLACE AND WAYS TO IMPROVE THEM

I commend this House Subcommittee for holding these hearings on these matters at a time when our military is not facing an immediate threat of chemical or biological weapons. The calmness of our discussions today is in sharp contrast to the sense of excitement and urgency prior to the Gulf

War. Now is the time to establish procedures for the use of drugs or biologics to defend against chemical or biological weapons. We should not have to invent a process to grapple with difficult choices when we are already in crisis.

As I understand the new safeguards that have been put in place by statute, by FDA regulation, and by the President's Executive Order it seems that we have come a long way toward establishing that process. However, more needs to be done. My suggestion accompany a brief description of each safeguard.

A. FDA has stated that the DoD should, use a waiver of consent rarely and only on condition that other safeguards are met. That means, among other things, that DoD must pursue the testing of drug development for use against chemical or biological warfare in a measured and consistent fashion in peacetime as well as in time of national danger. DoD must not wait until the crisis is imminent before requesting FDA approval. Furthermore all of the available information should be summarized in terms understandable to non-experts and transmitted to military personnel in a timely manner.

Comment: ***No one can disagree with the FDA recommendation. Testing in animals, and evaluation of other uses of these drugs is extremely important. DoD can do a much better job of this than it did in 1990. All training manuals should be updated in the light of ongoing research results. Nevertheless, because no drug can be tested under battle conditions, hard decisions will still have to be made in time of crisis. We will never have enough data to make a decision to require a drug a simple or easy choice.***

B. Only the President may waive informed consent.

Comment: ***We must realize that in a situation similar to that faced with Iraq, Bosnia, or Kosovo, the President must lead the people to approve the proposed action. In other words, the President must believe in the importance of the military action to be taken, and must convince a critical mass of the nation that the proposed military action is an appropriate step for the U.S. to take. Consequently the President is almost certain to have a bias in favor of any step that portends to strengthen our military personnel for combat. Leaving the decision to the President does not, therefore constitute a strong safeguard. The President should be informed of the discussions as well as the recommendations of a properly constituted IRB before making the final decision. If possible the President should be briefed by the IRB so that IRB concerns will be fully and accurately communicated. The IRB should include some military personnel, but it should should be created, not by DoD but by FDA. IRB members should include non-military experts and non-military lay persons. It should be chaired by someone outside the military. A IRB recommendation not to waive informed consent should be binding -- even on the President.***

C. An IRB should review all aspects of the IND and the waiver proposal.

Comment: ***An Institutional Review Board (IRB) constituted by FDA expressly for the purpose of reviewing drugs or biologics that can never be fully tested for use in battle conditions should be convened. Unlike the 1990 FDA committee, the IRB should have security clearance so that it will know the actual plans and the conditions that are expected to prevail when the compounds are utilized. The IRB members should include, not only military physicians and scientists, but civilian physicians and scientists. It should have a number of non-military, non-scientists as well. Military personnel should constitute no more than one third of the IRB. The IRB should review the information that is to be provided to military personnel, and the means by which it will be provided. Memoranda, training sessions, training manuals, training films etc. shall be reviewed by the IRB as part of the consent process. The IRB should take responsibility for the accuracy and readability of all information disseminated about the proposed drugs.***

Additional Comment: ***a Data and Safety Monitoring Board (DSMB) should be created that will have ongoing responsibility for tracking each individual who receives the drugs or biologics, for evaluating each adverse event in each recipient, and for collating this material into a report that shall be forwarded to the IRB and to the President at regular intervals. Similarly, the DSMB shall collect all pertinent data relevant to the effectiveness of the drugs or biologics. The DSMB should be assisted by a cadre of scientists, statisticians, and data managers who are charged with seeing that data are collected in a timely fashion, in a consistent manner, by all units administering the drugs or biologics. Each testing unit that receives these drugs or biologics should designate one or several persons whose primary responsibility is to see that data is collected in a timely and useful manner. Both the IRB and the DSMB should be established and functioning prior to the time of crisis. They must review, approve, and monitor the testing of drugs and biologics before a crisis arises. Outside of a national crisis, both the IRB and the DSMB should demand, among other safeguards, that a careful process of information conveyance and uncoerced consent characterize these studies. Consent auditors commissioned by the IRB should observe the process of consent.***

Mr. Chairman, that concludes my prepared remarks. I will be pleased to answer any questions that you may have.

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 pre-

ventive 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 rel-

atively 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 only 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.]

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