





HEALTH AFFAIRS

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

NOV 29 1997

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration
Department of Health and Human Services
Rockville, Maryland 20857

Attn: Documents Management Branch (HFA-305)
Re: Docket NO; 90N-0302

Dear Dr. Friedman:

This letter provides Department of Defense (DoD) comments on the July 31, 1997, Federal Register notice soliciting comments on the Interim **Final Rule** of December 21, 1990, authorizing **the Commissioner** of Food and Drugs to determine **that obtaining** informed consent for the use of investigational new drugs in certain **military** combat exigencies is not feasible. We feel the prime objective should be to allow medical personnel to use the best **prophylactic** and therapeutic products available to **protect** military members against **chemical and biological weapons** and other **operational** medical **threats** and to protect disaster response personnel and the public in **the** event of domestic terrorism use of **chemical** and **biological** weapons. We offer three primary **points** in support of maintaining the "**military** combat exigency" **rule**.

1. We must keep faith with the President's commitment that "we will always, always **do everything we can** to protect our own."

Consideration of the military **combat** exigency rule **should** be guided **primarily** by the need to protect military forces. There are undoubtedly *numerous* compliance issues concerning "investigational new drug" (IND) rules in military combat operations, and many of these are indeed important. But they are secondary to the primary issues of the **life** and **health** of military members in high **threat** situations. The review of the interim **final rule** should **start** with a commitment to allow medical personnel to use the best prophylactic and therapeutic products available to protect military members against chemical and biological weapons and **other** operational medical threats.

2. The **need** to "**protect** our own" extends to the **threat** of foreign and domestic terrorism **involving** use of chemical or biological **weapons** against military personnel or **civilians**.

Khobar Towers, the World Trade Center, Oklahoma City, and the **Tokyo** Subway are reminders of **the** need for preparedness against terrorism. The DoD is

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required by **Presidential Decision** Directive 39 to **support the Department of Health and Human Services** in **making** available **DoD stockpiles** of **unique medical products** in the event of a domestic terrorism use of **chemical** or **biological** weapons. The medical response to such an event — whether against military or civilian targets — may include **the treatment use** of **products** not approved by **the FDA** for **general commercial** marketing. The **ability** to use these "**investigational new drugs**" in this context may be critical to saving lives, perhaps many, many lives. In a **large** emergency response operation, **as** in a large military combat operation, **compliance** with **all** of **the** normal FDA rules for **INDs** — rules designed **primarily** for **clinical** research **trials** — may be quite **infeasible**. **If** the best **treatment** available to save lives is an **IND** product, use should not be hindered by non-feasible **regulatory compliance** requirements. The responsible Federal agencies **should** be guided by the prime objective of **allowing** medical personnel to use the best prophylactic and **therapeutic** products available to protect **military** members against **chemical** and **biological** weapons and other operational medical threats and to protect disaster response personnel and **the** public in the event of domestic terrorism **use** of **chemical** and **biological weapons**.

3. The ability to "protect our own" requires a range of viable options for the President and other senior officials to consider in a military or civilian emergency, including the option of determining that informed consent and other normal IND requirements are infeasible.

How the responsible agencies achieve the **prime** objective of allowing medical personnel to use the best products **available** depends on the **circumstances** of the exigency presented. There needs to be a range of potentially viable options **that can** be considered by the President, Secretary of Defense, Secretary of **Health** and Human Services, and other officials to meet the prime objective in military or **civilian** terrorism exigencies **that** may arise. For particular scenarios, options might include: use of approved **products** only; use of **IND products** under **all IND rules**; use of **IND** products with waivers of many **IND** rules; and perhaps **special** product approvals for **emergency** uses only. One of the options that **should** remain **available** is the use of **an IND** product under a determination that **normal IND rules**, including informed **consent**, are infeasible. **DoD** would prefer, as **FDA** undoubtedly would, that this **option** not be used. However, we **strongly** believe the authority of the current rule must be maintained as an option.

Finally, we look forward to the results of our joint **FDA/DoD/OEP** working group charged to develop a range of **potentially viable** options for achieving the prime objective of **allowing** medical personnel to use the best prophylactic and therapeutic products available to protect military members **against chemical** and **biological weapons** and other operational medical threats and to protect disaster response personnel and the public in the event of domestic terrorism use of **chemical** and **biological** weapons. This is a **difficult** challenge, one not likely to produce in the **near** term an "perfect solution." Therefore, we suggest the work group **concentrate** on developing a range of **potentially viable options** that could be **considered** by the President, Secretary of Defense, Secretary of **Health** and Human Services, and other officials to meet the

Secretary of **Health and Human Services**, and **other officials** to **meet** the **prime objective** in **military** or civilian terrorism exigencies that may arise **in the near term**.

Attached are **DoD** response5 to the **questions** posed in the Federal Register notice. Also, to **supplement** the public record, we resubmit our comments of **September 13, 1996**, and enclose a copy of the 1996 **testimony** of Dr. Edmund Howe to the Presidential Advisory Committee on Gulf War Illnesses **concerning the ethics** of the military combat exigency rule.

Thank you for your assistance in **these matters** over the past few **months** and for your consideration of **DoD** comments on **this** important **national security** issue.

Sincerely,



Edward D. Martin, M.D.

Acting Assistant Secretary of **Defense**

Attachments:

1. **DoD comments** on questions posed in Federal Register notice.
2. **DoD** letter to FDA of **September 13, 1996**.
3. **PACGWI** 1996 testimony of Dr. **Edmund** Howe.

**Department of Defense Comments
on FDA Questions Regarding Interim Final Rule**

*Issue A: Questions regarding **the** interim rule.*

*A. (1) Should the agency **revoke** the interim rule? **If** so, why?*

The Department of Defense considers it a national defense requirement that **the** authority of the military combat exigency **rule** be **maintained**.

*A.(2) Are there circumstances under which use of the **interim** rule would be justified? **If** so, what are those **circumstances** ?*

The circumstances under which use of the military combat exigencies rule is both **justified and** required are **that** based on the best evidence of safety and efficacy of a drug or vaccine, **the degree** of peril posed by the **threat** for which the drug or **vaccine** is indicated, and the absence of **a** satisfactory alternative therapy, failure to use the drug or vaccine will, regardless of **the personal** preferences of **the military** member, be contrary to the best interests of **the** member, endanger other personnel in **the** unit, and risk failure of the military mission.

Implicit in this answer are three points which, at **the** risk of redundancy, bear explicit underscoring. First, the military purpose is force protection, not data collection. Stated another way, it is medical **treatment**, not medical research. Second, the drugs and vaccines involved will be safe. The evidence of safety will be comparable to that for drugs and vaccines approved by **FDA** for general **commercial** marketing. They are not exotic, experimental drugs. Third, the reason these products are **classified** as “investigational new drugs” -- **i.e.**, the reason **they** have not been approved by **FDA** for **general** commercial marketing -- is that efficacy **has** not been proven in controlled human clinical trials, which is the normal FDA standard for drug approvals. **But** apparent efficacy will be established by results of animal **trials** and other means. **Stacked** against **the** degree of peril and absence of an alternative, the evidence of safety and efficacy -- even if less **than that** necessary for **FDA** approval for general commercial marketing throughout the United States -- is **sufficient** for FDA approval for standardized use in the military combat exigency.

*A. (3) The interim rule is based on the premise **that** informed consent is not **feasible** in military combat exigencies because **if** a soldier were **permitted** to say “no,” this could jeopardize the **individual** soldier’s **life**, **endanger** other personnel in his or her unit, and jeopardize the accomplishment of the combat mission. **DoD** has **alleged** that it is **not an option** to excuse a nonconsenting **soldier from** a military mission. Given the experience in the **Gulf** War, does this rationale still hold?*

The use of **the** military combat exigencies rule during the Gulf War was to help protect American military **personnel** from the enemy’s horrific arsenal of chemical and

biological weaponry. The most important “experience in the Gulf War” was **that** the enemy chose not to use this arsenal. If there is a basis for confidence that every potential adversary in the future **would also** not use such weapons, then the rationale for the military combat exigencies rule would not “still hold-”

The problem is that **the** world community has clearly documented very aggressive chemical and biological weapons programs in North Korea, China, **Iran**, Iraq, Libya, Russia, and **possibly** other countries. In a future conflict, the United States will have four options:

Option 1: To assume **the enemy** will not use chemical or biological weapons, and, therefore, to eschew medical countermeasures.

Option 2: To excuse military personnel who chose not to use the medical protection, both respecting their individual choice and saving them from danger.

Option 3: To allow individual military members to decide on the use of medical **countermeasures**, but with the selection having no impact on the individual’s **responsibility** for the mission.

Option 4: To make standardized use of a drug or vaccine, when **indicated** by the best evidence of its safety and efficacy, the degree of **peril** posed, and the absence of a satisfactory alternative therapy.

The respective risks of each option must be considered. If option 1 is chosen, **and** the assumption turns out to be wrong, there could be horrendous consequences—Under option 2, the **predictable** consequences in any major scale **military** operation, are a large number of abstentions, grave danger for remaining members who choose to **carry** out the mission, and military **failure**. If option 3 is chosen and the enemy uses chemical or biological weapons, those who declined **medical** protection **will** be at great risk, as will others in their units who **rely on** them and the accomplishment of the aspects of the **mission** for which they were responsible. If option 4 is followed, and it turns out that the enemy does **not** use **the** weapons, the drugs or vaccines would have been received **unnecessarily**.

At this juncture, it is not necessary for the Secretary of Health and Human Services to decide that option 4 is the most prudent course — only **that** it should be **an** option; that it *might be the best* option under *some circumstances that might arise*. For it to be **an** option, the military combat exigency rule **must** be maintained.

A. (4) *Instead of waiving **the requirement** for informed consent, is it feasible to obtain **anticipatory** consent from military personnel during peace time for the future use of **investigational products** during a **military conflict**? If it is feasible, would such **consent** be valid as “informed consent”? **What would be the needed consent algorithm to make it valid and feasible?***

It is unclear what “anticipatory consent” means. For example, is it a subset of option 2 or option 3, as described in the comment to the previous question? The **primary** issue is not the proximity of the consent to **the** use of the drug or vaccine, but whether the military command authority **can** order **military** personnel to use a drug or vaccine under the extremely limited circumstances described in the comment to question 2, above, and covered by the current military combat exigency rule. If the concept of “anticipatory consent” means providing information and training to military **personnel** in **advance** of contingency operations, **this** is very **desirable**.

A. (5) *Instead of **waiving** the requirement for informed consent, is it **feasible** to obtain anticipatory **consent** from military **recruits** (**prior to their recruitment into the military**) for the **future** use of **investigational** products during a military conflict? **If it is feasible**, would such **consent** be valid? **What** would be the needed **consent** algorithm to **make** it valid **and feasible**?*

Again, the **meaning** of “anticipatory consent” is not clear. In a **very** real sense, under the **all-volunteer** military force, the act of volunteering for military service is consent to be subject to command authority for the conduct of military **operations**. It is well understood that this command authority can order an individual to do things that **may** result **in** the loss of the individual’s **life**. It is also **well** understood that the autonomy enjoyed by civilians **in American** society is **significantly** sacrificed in the specialized society of the military. To the extent the **conduct** of military operations includes requirements to take drugs or vaccines **when** indicated by the best evidence of **safety** and efficacy, the degree of peril posed, and the absence of a **satisfactory** alternative therapy (whether or not those products have been approved for general commercial marketing in the United States), this is subsumed by **the** obligation **freely** accepted — legally, ethically, and **practically** — by every military member.

If the point of the question is whether **informed consent** similar to that under 21 CFR Part 50 is **feasible**, the answer is **that** it is not. Among, the reasons is that the regulations disallow any penalty for declining to use an **IND** product, as well as assure the **right** to **withdraw** consent at any time. If declining means the individual who wants to join the military will **not** be accepted, the “**voluntariness**” of the consent will not meet the regulatory requirement, nor would irrevocable consent. **In** addition, providing detailed information regarding a variety of possible threats and medical countermeasures a recruit might face during a period of military service is not **feasible**.

A. (6) ***If** the **interim** rule is needed, are there **changes that should be made** to it based on experiences during and following the Gulf War? **If** so, what are these changes and **why** should they be made.*

The **Department** of Defense has no changes to recommend based on experiences during and following **the** Gulf War, **but** welcomes the opportunity to **consider** changes **suggested** in the public comment process.

A. (7) ***Can** or should **the** interim tie be narrowed in scope? **If** so, **how**?*

The scope of the rule should not be narrowed. It **should** be broadened in two ways. First, it should be explicit that military operational exigencies other than combat are covered within the scope of the rule. For example, protection against a terrorist attack, such as that at Khobar Towers last year, or an endemic disease **threat** in a peacekeeping or **humanitarian** operation might meet the criteria of the rule and **should** be covered. Second, the issue of medical countermeasures against **the** threat of domestic terrorism involving **chemical** or **biological** weapons should be considered.

A. (8) *If the rule were to be re-proposed:*

(a) *Should there be a requirement that DoD's proposed use of investigational products(s) be approved by an **IRB that is independent** of DoD? If so, why should **DoD** be held to a **requirement** not imposed on other **institutions**, and what should be the **requirement** for **that independent IRB**? Can this be accomplished without compromising military or national **security**?*

Under the law, the chain of command for military operations “runs — (1) from the President to the Secretary of Defense; and (2) from the Secretary of Defense to the commander of the combatant command.” 10 U.S.C. § 162. The Department of Defense does not support the diversion of command responsibility to a review board. It should be noted that the use of the **military** combat exigency rule requires a determination by the Commissioner of Food and Drugs, who is independent of **DoD**.

(b) *Should the authority to **make** the “**feasibility determination**” (i.e., whether obtaining **informed consent** is “**not feasible**”) under the **interim** rule be vested in persons or entities other than the Commissioner of **FDA**?*

The Commissioner of the FDA is the appropriate official for **the** feasibility determination.

(c) *Should the **rule** be more specific in describing the **information that** must be supplied to **military** personnel, or should **FDA** have **wide** latitude to **make** such **determinations** on a case-by-case basis?*

The items of information to be provided to **military** personnel should be agreed upon by the **DoD** and **the** FDA on a **case-by-case** basis. Information should address: the nature and degree of **peril** against which the drug or vaccine is designed to protect; safety and efficacy of the drug or vaccine; contraindications **and** side-effects; and alternatives treatments.

(d) *Should additional measures be taken **to** insure that **information** required by FDA is **effectively** conveyed to the affected military personnel? If so, **what** should these **measures** be?*

No changes to the regulation are required in this regard. At the time the determination is requested that informed consent is **not** feasible in a **particular** military combat exigency, **DoD** should provide its plan for the dissemination of information.

*(e) Should the rule address what **constitutes** adequate **record-keeping** and **adequate** long term **follow-up** of individuals who receive investigational products? If so, in what way?*

The rule need not more specifically address record-keeping for the use of investigational products. Issues of record-keeping and follow-up are already **covered in** existing FDA regulations and guidelines, including the rules for the **treatment** use of **INDs**. **DoD** and FDA should work toward a mutually satisfactory resolution of feasible record keeping requirements- This work **can** take account of ongoing **DoD** initiatives to develop **automated** record keeping and **immunization** tracking systems. These should **facilitate** record **keeping** and follow-up for approved products and **INDs**, even in operational settings-'

*(f) Should the rule contain **additional** procedures to enhance **understanding, oversight, and accountability**? If so, **what** are these procedures?*

DoD believes internal military procedures for understanding, oversight, and accountability have been and will continue to be strengthened. These matters, however, are separate from the decisive factors pertinent to the issue of the feasibility of informed consent under certain military **combat** exigencies.

*(g) Should the rule contain **additional** procedures to **track** noncompliance?*

Validation of compliance is an important matter for **DoD** to assure. However, no changes in the regulation are needed concerning this matter.

*Issue B: When is it ethical to expose **volunteers** to toxic chemical and biological agents to test the **effectiveness** of products that **may be used to** provide potential protection against those agents?*

The products under development are to be used to protect service members against **lethal** exposure to chemical and biological **warfare** agents. It is never **ethical** to expose volunteers to such **lethal** amounts of these agents in order **to** test the potential effectiveness of pre-treatment, **treatment** or prophylactic products.

Dose or **concentration** ranging studies are normally required for new or **new-**indication studies of drugs or **biologics**. Because response to **treatment** of sub-lethal doses of chemical or biological **agents** (weapons) could not be **extrapolated** to predict response to higher doses, a **lethal** dose would be necessary to test **the** efficacy of the protective drug or biologic. If **lethal** doses were given to volunteers, a 100% effective

rescue agent would need to be **available**, in **case** the protective agent failed and a **potentially** fatal toxicity had to be reversed. Antidotes **to** probable threat agents do not currently exist.

*Issue C: If products that may be used to provide potential protection against **toxic** chemical and biological agents **cannot** be **ethically** tested in **humans**, what evidence would be needed to demonstrate their **safety** and **efficacy**?*

*C(1). Should **FDA** identify the **evidence** needed to **demonstrate safety** and **effectiveness** for drugs that cannot ethically be tested on humans **to** demonstrate **efficacy** when such tests would involve administering a severely toxic substance **to** human **volunteers**? **If yes, what** should constitute the evidence needed to demonstrate **safety** and **efficacy**?*

Safety and efficacy data from **well-controlled** animal studies can serve **as** the basis for approval of certain drugs or **biologics** for humans. Four requirement categories for generating safety and **efficacy** data are provided.

1. **Animal** studies should **clearly** show **efficacy**. A validated animal model should be selected which has biological and mechanistic relevance to humans for the **toxicology of the** compound and the pharmacology of the **antidote**.
2. Animal studies should show a functional relationship between a surrogate marker and efficacy. A change in the surrogate marker should reflect a change in efficacy-
3. The surrogate marker needs to reflect the pathophysiology of the **toxic** process.
4. The surrogate marker should be measurable in humans. The drug or biologic agents should produce in humans **the surrogate** endpoint that would **indicate detoxification** of the **chemical** or biological weapon. The kinetics and/or **pharmacodynamics** of the drug or vaccine should be sufficiently understood to allow estimation of an effective dosing regimen in humans.

In addition, other information should be **obtained** in order to better **understand** and perhaps predict the reactions of the drug **or** vaccine when given to a large group of **DoD** personnel. These **might** include metabolic and disposition pathways in both the animal model and **in** humans and population studies in humans to understand **clinical covariates** to predict response ranges in very **large** groups.

*C(2) **If the agency** were to **identify** the evidence needed **to demonstrate safety** and **effectiveness** of these products, would **this** preclude the need for the interim rule? **What specific advantages** would this **offer** over the interim rule?*

Not completely- There will always be a requirement for the interim rule. Even if safety and efficacy benchmarks were identified by the agency for the products **under** development today, until **these** products were actually **licensed** or approved, they would still be investigational.. The clear threat of new chemical and biological weapons being developed makes the search for protective agents a continuous process. In the DoD's efforts to **continually** improve medical **care** and to counter new chemical and biological threats, there will always be products in development which will not have yet reached sufficient **maturity** to be **licensed** or approved. These products may still require *use* while they remain in **an** IND status, in which **case** use in connection with military combat exigencies may raise an issue regarding de feasibility of informed consent.

*C(3) Civilian populations may **require products** used in **the prevention** or treatment of the serious or **life-threatening effects from** exposure to toxic chemical or biological agents, e.g., in the **event** of exigencies such as **the** release of toxic chemical agents in the **Tokyo** subway system **Thus**, should the **agency** consider **identifying** the evidence needed to demonstrate safety and **effectiveness** for these products which would apply to both civilian as well as **military populations**?*

The Office of Emergency Preparedness, **DoD**, and the FDA **should** work together to assure that medical personnel **can** use the best prophylactic and therapeutic products available against chemical and **biological** weapons in both the military and **civilian** contexts. This should be an urgent priority-

STATEMENT BY

EDMUND G. HOWE, M-D., J.D.

PROFESSOR OF PSYCHIATRY; DIRECTOR OF PROGRAMS IN MEDICAL ETHICS
(UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES)

BEFORE THE

PRESIDENTIAL ADVISORY COMMITTEE

ON GULF WAR VETERANS' ILLNESSES

USE OF INVESTIGATIONAL DRUGS AND VACCINES IN THE GULF WAR
ETHICAL CONSIDERATIONS IN WAIVING INFORMED CONSENT
FOR MILITARY EXIGENCIES

JANUARY 12, 1996

NOT FOR PUBLICATION .
UNTIL RELEASED BY
PRESIDENTIAL ADVISORY COMMITTEE
ON GULF WAR VETERANS' ILLNESSES

USE OF INVESTIGATIONAL DRUGS AND VACCINES IN THE GULF WAR

ETHICAL CONSIDERATIONS IN WAIVING INFORMED CONSENT
FOR MILITARY EXIGENCIES

Mr. Chairman, distinguished Members of the Committee, I am Edmund G. Howe, M.D., J.D., Professor of Psychiatry and Director of Programs in Medical Ethics at the Uniformed *Services* University of the Health Sciences. I appreciate the opportunity to discuss with you today the exceedingly difficult ethical questions which arose in regard to the use of protective agents in the Persian Gulf. When the DOD first anticipated that Iraq might use chemical and biological weapons, the DOD was aware of the profound ethical dilemmas this situation posed.. Consequently, the DOD immediately sought consultation from other governmental agencies and civilians outside the DOD with special expertise in medical. ethics.

One of the parties with whom the DOD conducted extensive discussions was the. Office for Protection from Research Risks (OPRR/NIH). The OPRR is responsible for monitoring and protecting the health and welfare of humans and animals when they are used as research subjects in behavioral and biomedical research supported by the Public Health Service. Guidance from the OPRR was particularly valuable to the DOD's understanding of the ethical issues involved pertaining to research. The OPRR pursued extensive ethical discussions with civilian ethicists throughout the process

benefits the servicepersons serving with them. Servicepersons understand that they may have to sacrifice any number of personal interests during combat and, implicitly, they agree to make such sacrifices if this is necessary when they enter the military-

This shift from the usual ethical priorities adopted by civilians during peacetime is exemplified by the principle of military medical triage. Normally during emergency situations medical careproviders give highest priority to saving the lives of those patients who are worst off, During combat, military physicians are expected under extremely rare circumstances to do the opposite. Namely, they are expected to shift: priorities and treat servicepersons who are better off and can return to battle if and when this seems necessary to further the likelihood of success of the military's mission. In actuality, this hardly ever occurs. In principle, however, this shift is radical. It is this same kind of shift in regard to the use of protective agents which was necessitated by the threat of Iraq's using chemical and biological warfare against our troops.

The underlying ethical justification for this rare and radical shift in priorities is that unless the customary values are sacrificed, far greater wrongs may occur: these may include one country taking over another and harming *its* people, genocide, and even the destruction of this nation and its people. The different: priorities in the military during combat, accordingly, are not established by the military but are established by and represent the country whose interests it serves.

Servicepersons' priorities differ, then, from civilians' in

that their individual interests are subordinated to those of the mission and their unit- Thus, although it would be in servicepersons' individual best interests to *not* fight when they are ill, as from malaria or dysentery, commanders may send them to the front, regardless of their illness, if this is necessary to benefit the mission or other servicepersons. Similarly, if an individual serviceperson did not want to carry a canteen, wear protective clothing, or he vaccinated against an endemic disease, the commander could not permit this serviceperson to exercise autonomy in this manner since this would unnecessarily endanger the serviceperson and, consequently. the mission and other servicepersons in the unit.

Servicepersons are aware that *as* they approach actual fighting, their autonomy dramatically may decrease. They understand that their commander may order them to enter life-threatening situations under enemy fire, and make any number of other decisions to benefit the mission or the unit- These may include their commanders requiring them to make use of protective devices during combat.

As I already have stated, when servicepersons join the military, they agree to subordinate their own interests and autonomy to the military when necessary for the mission or their unit. This promise is also reciprocated, however, by the military. The military, in turn, promises all servicepersons that it will protect their lives during combat to the maximal degree that this is possible, contingent, of course, on its fulfilling the needs of the mission.

..... Ethically, there are basically four arguments that servicepersons should take protective agents without being given the opportunity to refuse to consent: First, this is necessary to maximize the likelihood that the US military effort will succeed. As stated, if US troops were decimated after Iraq used chemical or biological weapons, hardly imaginable harms to persons in other countries and this one could occur. Second, this is necessary to protect inordinate numbers of servicepersons' lives which would be lost if Iraq used these weapons. Third, this is necessary for all servicepersons to fulfill the implicit promise they have made to other servicepersons that they will sacrifice their lives if necessary for the mission or their benefit- In this case, of course, the sacrifice required to save the mission or other servicepersons is not their lives but their autonomy to refuse to consent to taking these protective agents. Fourth, this is necessary for the military to fulfill its promise to all servicepersons to do everything possible to protect their lives;.

What are the opposing arguments? First, it can be argued that protective agents which have not been fully tested should not be given at all- Whether these agents should be given should depend primarily on whether these agents most likely would save large numbers of servicepersons' lives if Iraq used chemical or biological weapons, but do little harm if Iraq did not. As stated, when the possible need for protective agents initially became apparent, medical experts in the DOD and FDA reviewed the available data on the effects of these agents on humans in other contexts and on animals. On the basis of this review, the DOD determined that

for the agents considered, the probable benefits were overwhelming and the expected adverse *risks*, minimal- If this had not been the case or if the benefit/risk ratio had even been significantly closer to marginal, the justification for using these agents would have been, of course, increasingly problematic.

Second, it can be argued that even if these agents should be available, *servicepersons* should be able to ^{refuse} to take them- If *servicepersons* could refuse consent, this would respect their autonomy, but *several* important values would be violated- That is, if *servicepersons* were permitted to refuse to consent, two options would be possible: *Servicepersons* who refused *consent* could be excused from combat altogether or they could remain in combat without their being protected by these agents.

If *servicepersons* were excused from combat, this could result in US troops becoming significantly depleted. This could jeopardize the success of the *mission* and increase the danger to *servicepersons* who remained in combat. *Further*, if consenting *servicepersons* remained in combat, this would violate the ethical principle of justice or equity- That *is*, those who took the agents would still risk being killed during combat by normal *weapons*; those who did not take these agents and, therefore, were *removed* from combat would not.

If, on the other hand, *servicepersons* who refused consent remained in combat without these protections and Iraq used chemical or biological weapons, the *servicepersons* without protection would be much more vulnerable to illness and death. Again, as a result of the depletion in their numbers, the *success* of the mission could be

threatened and servicepersons taking protective agents more greatly endangered. They would be additionally endangered if they attempted to help these servicepersons.

Fortunately, the degree to which these agents would protect servicepersons from the effects of chemical and biological weapons was never tested in the Persian Gulf. Yet, investigations following the war have indicated that Iraq had these weapons ready for use, It may have been only because Iraq falsely believed that the US would retaliate with nuclear weapons that Iraq decided not to use them. Our information regarding the weapons Iraq could have used was accurate. For example, Iraq was prepared to deliver botulism, a highly lethal disease, by missile attack. Botulism vaccine was one of the protective agents given to servicepersons.

Thus, this chilling question remains: What would have happened if Iraq had used these weapons and U. S. forces had not had as much protection as possible? The grim outcome which can be imagined supports the *wisdom* of the ethical judgements actually made. It suggests as well, several new needs, such as to insure that servicepersons are protected as much as possible in the future and to establish means by which other countries' forces, captured enemy servicepersons and civilians can be protected as well. These initiatives may go beyond the scope of this discussion, but, hopefully, will be among the ethically important outgrowths of this meeting.



HEALTH AFFAIRS

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

SEP 13 1996

Honorable David Kessler, M.D.
Commissioner of Food and Drugs
Department of Health and Human Services
Rockville, Maryland 20857

Dear Dr. Kessler:

On behalf of the Department of Defense, I submit comments on the petition filed May 7, 1996, by Public Citizen Litigation Group requesting that the FDA repeal 21 CFR § 50.23(d), which allows the Commissioner of Food and Drugs to determine that obtaining informed consent for the use of an investigational new drug is not feasible under certain military combat exigencies.

Granting this petition would jeopardize the lives and health of military personnel and weaken national defense. The Department of Defense urges that it be denied.

The DoD comments are set forth in the attachment- To briefly summarize, when the President orders the deployment of U.S. military forces, the U.S. Government has a duty to take all reasonable precautions to bring about a successful completion of the mission and a safe return of the forces. In today's world, that duty must include a recognition of the startling proliferation of chemical and biological weapons among potential adversaries and terrorist organizations and an obligation to implement the best possible medical countermeasures. Implementation of the best possible medical countermeasures may require the standardized treatment use of an investigational new drug or vaccine for all personnel at risk in a military combat exigency. The current rule's authority to do this is extremely limited, available only under extraordinary circumstances and explicitly restricted to advancing the best interests of the military personnel concerned. The current regulation fully complies with applicable law and governing ethical standards.

Overall, notwithstanding some difficulties in carrying out the designed treatment protocols, the uses of the current rule during the Persian Gulf War clearly support the rule's

continuation. It was used only twice, both times for well established drugs about which very strong evidence of safety and efficacy was documented, It was never used for exotic or "experimental" drugs. Finally, DoD initiatives since the Gulf War, including those taken for Operation Joint Endeavor in Bosnia, have improved our ability to implement medical countermeasures under the authority of the current rule, should that become necessary in the future-

It has been nearly six years since the current rule was approved by the Secretary of Health and Human Services in anticipation of imminent hostilities in the Persian Gulf War. The rule was accepted by the courts, by Congress, by the press, and by the public, Remaining dissenters are few, and are unencumbered by any responsibility for the lives and safety of the personnel sent by the President into military operations. Even with critical hindsight, the interim final rule stands today as a scrupulously limited, well justified authority. DoD remains quite interested in working with the FDA on possible refinements to the rule and improvements in implementation procedures, as well as on methods to expedite approval of appropriate drugs and vaccine's needed for military operations.

We cannot predict the next occasion on which the President will determine that the national interest requires the deployment of U.S. military personnel, nor the exact threats they will face. We can, however, predict that the best medical countermeasures may well include the treatment use of an investigational new drug. And we can be certain of our duty to provide the best medical countermeasures available, For these reasons, the Department of Defense believes it is a national defense requirement that the authority of the current rule be maintained.

We urge that the petition be denied.

Sincerely,



Stephen C. Joseph, M.D., M.P.H.

Attachment

DEPARTMENT OF DEFENSE COMMENTS ON
PUBLIC CITIZEN LITIGATION GROUP'S PETITION TO REPEAL
INTERIM RULE ON ~~THE TREATMENT~~ USE WITHOUT INFORMED CONSENT OF
INVESTIGATIONAL ~~NEW~~ DRUGS IN MILITARY COMBAT EXIGENCIES

The Department of Defense respectfully submits the following statement of reasons for urging that the petition to repeal the interim final rule be denied.

1. When the President commits U.S. military forces to a combat, peacekeeping, or humanitarian deployment, the U.S. Government has a duty to take all reasonable precautions to bring about a successful completion of the mission and a safe return of the deployed forces.

Following the terrorist bombing in June at the U.S. facility in Dhahran, in which 19 were killed, many critical questions have been asked of senior government officials about whether adequate precautions had been taken to protect these military members. It is predictable that such questions will be asked any time there are deaths and injuries that appear in hindsight to have possibly been preventable. This arises from the duty felt by the people to support deployed military forces whose responsibility it is to carry out missions ordered by the President. That support includes an expectation that the Department of Defense and other agencies of the U.S. Government recognize their duty to take all reasonable precautions to promote the successful completion of the mission and the safe return of the military members.

A vital part of that duty falls to the medical establishment of the Government. In preparing to meet that duty, scenarios involving hundreds or thousands of potential casualties and the precautions that should be taken must be considered. This responsibility to consider threats and precautions is not exclusive to the Department of Defense. Expertise and authorities of other agencies are often implicated, and when they are, these agencies share in the Government's duty to the military forces. Any breach of that duty by DoD or any other involved agency invites a potential calamity.

2. The Government's duty to take all reasonable precautions to preserve the fighting force **must** include recognition of the startling proliferation of chemical and biological weapons among potential adversaries and terrorist organizations and an obligation to implement the best possible medical countermeasures.

In a recent report¹ on the proliferation of weapons of mass destruction, Secretary Perry wrote:

We received a wake-up call with Saddam Hussein's *use* of SCUD missiles during Operation Desert Storm and new information on his ambitious nuclear, biological, and chemical weapons programs. The proliferation of these horrific weapons presents a grave and urgent risk to the United States and our citizens, allies, and troops abroad. Reducing this risk is an absolute priority of the United States.

* ☒ ☒ * •

. . . . The bad news is that in this era the simple threat of retaliation that worked during the Cold War may not be enough to deter terrorists or aggressive regimes from using nuclear, biological, and chemical weapons. . . . The bottom line is that, unlike during the Cold War, those who possess nuclear, biological and chemical weapons may actually come to use them. The increase in the likelihood of regional war in today's world raises the risk.

This new danger requires new thinking and new leadership on how to prevent, deter and, if necessary, respond to the threat. . . .

This Report goes on to document very aggressive chemical and biological weapons programs in North Korea, China, Iran, Iraq, Libya, Russia, and possibly other countries. In addition, there have been warning signs regarding activities of terrorists and insurgents, including the 1995 nerve gas attack in Japan. The

¹ "Proliferation: Threat and Response," Office of the Secretary of Defense, April 1996.

Report concludes:

The character of warfare has changed. Just as military planners must assume that antagonists may have armored forces and combat aircraft, planning for major regional conflicts must give consideration to the possibility that adversaries may have NBC [nuclear, biological and chemical] weapons and the means to deliver them,

When such consideration is given to this possibility, attention must be focused on identifying the best possible medical *countermeasures* to the biological and chemical weapons threat.

3. Implementation of the best possible medical countermeasures may require the standardized treatment use of an investigational new drug or vaccine for all personnel at risk in a military combat exigency, including those personnel who, for whatever reason or no reason at all, would prefer an alternate treatment or no treatment.

The need to determine the best possible medical countermeasures may lead *in* any of a number of directions, Most likely, the medical community will recommend reliance on well established preventive or treatment approaches using approved drugs and licensed vaccines. However, in some cases, there may be no such option available, In this regard., the development of prophylactic or therapeutic modalities for chemical and biological weapons threats is severely hindered by an inability to carry out human clinical trials of efficacy. Nonetheless, sufficient evidence of efficacy may be present using a combination of animal model trials and surrogate endpoint data on humans. When justified by the safety and efficacy data, DoD strongly favors approval of a New Drug Application and continues to believe that the FDA's accelerated approval process, including the option of marketing limitations, is an appropriate mechanism for addressing these special military needs.

In still other cases where the best possible medical approach includes the use of an investigational new drug, it may not be necessary, depending upon the nature of the risk and other factors, to use the investigational product on a standardized basis. For example, in the current Bosnia deployment, military

members are given the option of receiving tick-borne encephalitis vaccine; members are free to decline the vaccine-

However, it is also possible that the best medical countermeasures are products not approved by FDA for general commercial marketing for the specific purpose involved, that approval under the accelerated process is not practicable, and that because of the nature of the threat and the lack of alternatives, a failure to use a drug would endanger individual members, others who rely upon them to carry out their respective tasks, and the mission. The question becomes: what should be done in such cases? In the preamble to the interim final rule, the FDA, answered the question:

. . . . DoD has the right and responsibility to make command decisions that expose troops to the possibility of combat and has the concomitant responsibility to protect the welfare of these troops both individually and as a group. . . . FDA respects DoD's obligation and commitment to do everything possible to protect military personnel who may be exposed to potentially hazardous conditions. FDA further appreciates that this protection may include medical treatment or prevention with an investigational drug considered necessary to protect not only the health of individual soldiers but to ensure the welfare of the remaining forces. . . . Since these individual soldiers may be required to be exposed to combat, permitting them to choose whether to receive an investigational product that is the only available satisfactory protection against life-threatening conditions. is contrary to their individual best interests and to the welfare of the other soldiers involved. [Emphasis added.]

One might ask: why would military members decline recommended drugs or vaccines under these circumstances? The answer is that there could be many, many reasons. Individuals might decide that it is unlikely that chemical or biological weapons will be used, or that, if they are, protective gear will be sufficient. They might have heard rumors of side effects or "mystery illnesses" attributed to the drugs or vaccines. They might not believe information from command authorities based on disenchantment with circumstances particular or general. They might have seen media coverage of statements from "public

interest" advocates back home inappropriately accusing the military of wrongs comparable to Nazi medical experiments. They might be getting erroneous medical advice from friends or family. They might be confused by the first-time experience of having a choice regarding combat medical care. They might put off a decision until a later possible time or event. Moreover, if the choice is truly voluntary, they do not need a reason and may not have one. The fact is that there is no basis to assume that, among a group of many thousands of people presented with complicated medical information, most will chose the course all knowledgeable medical people would consider the only wise one. And in the middle of large-scale combat operations or preparations, communication and decision making processes are anything but ideal.

As an illustration of the problem, assume a deployment for a major regional conflict, such as the Persian Gulf War, involving 500,000 U.S. troops. Assume further a very good response rate of 80% of these troops providing voluntary informed consent for, to select an example, botulinum toxoid vaccine. If botulinum toxin weapons are used in large scale by the enemy, we will have 100,000 troops at considerable risk of fatal injury, with no alternative treatment available. This far exceeds the total number of U-S. forces killed in the entire Vietnam War- Failing to prevent preventable casualties of even a small fraction of this magnitude would be a human tragedy, a military disaster, and a national scandal of historic dimensions.

4. The current rule is an extremely limited authority, requiring case-by-case justification, available only under extraordinary circumstances, and explicitly restricted to advancing the best interests of the military personnel concerned.

As the FDA stated in the preamble to the current regulation:

. . . . Because of the paramount importance of informed consent, only the narrowest exceptions to this requirement are consistent with FDA's responsibilities and consistent with the best interests of human subjects. Nevertheless, FDA has determined that, in the special circumstance that may be created by the use of troops in combat and consistent with its obligations under sections 505(i) and 507(d) [of the Federal Food, Drug and Cosmetic Act], FDA may narrowly

expand the circumstances in which the Commissioner may determine that obtaining informed consent is not feasible.

Consistent with this policy, the current rule is an extremely limited authority. First, it does not: waive informed consent for the military, nor allow the military to do so. It does not even indicate that the Commissioner of Food and Drugs is inclined to find that informed consent is not feasible in military combat situations. It stands only for the proposition that it might be necessary under certain extraordinary circumstances to exercise the statutory authority to find that informed consent is not feasible because of military combat exigencies.

Secondly, quoting from the regulation (21 CFR § 50.23(d)(1)):

[DoD's] request must also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without *regard* to what might be any individual's personal preference for no treatment or for some alternative treatment.

Third, a duly constituted Institutional Review Board must have reviewed and approved the use of the investigational drug without informed consent. *Id.*

Fourth, the Commissioner must specifically find that "there is no available satisfactory alternative therapy." *Id.*

Fifth, the rule requires consideration of the "extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use." § 50.23(d)(2)(i).

Sixth, the context in which the drug will be administered must be considered. § 50.23(d)(2)(ii). A context involving one-

on-one treatment of an injured *or* sick patient by a physician is quite different from the administration of large-scale prophylactic treatment.

Seventh, consideration must be given to the "nature of the disease or condition for which the preventive or therapeutic treatment is intended," such as whether it is fatal. § 50.23 (d) (2) (iii) .

Eighth, the Commissioner will consider the nature of the information to be provided "concerning the potential benefits and risks of taking or not taking the drug." § 50.23 (d) (2) (iv). Even if consent is not required, comparable information will be provided.

Ninth, determinations that informed consent is not feasible because of military combat exigencies are time-limited, and may be revoked. § 50.23 (d) (4) .

Tenth, and most importantly, the "Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel." § 50.23 (d) (1) (emphasis added).

To repeal the regulation, as urged by the petitioners, would be a declaration that informed consent is never infeasible under military exigencies, including actual, effective use of weapons of mass destruction, which will have fatal effects, for which no alternative therapy is available, and in connection with which withholding the IND would be clearly contrary to the best interests of the troops.

5. The current rule is fully consistent with law and ethics.

The legality of the interim final rule was challenged in court by the same group that has now filed the current petition. The courts ruled that the rule is fully consistent with law. The District Court held:

The DoD's use of unapproved drugs does not involve the type of scientific investigation under controlled circumstances. that "research" connotes. On the contrary, the DoD has

responded to very real circumstances and chosen what it views as the best alternative given current knowledge. The primary purpose of administering the drugs is military, not scientific. The fact that the DoD will collect information on the efficacy of the drugs does not transform the strategic decision to use the unapproved drugs in combat into research. Furthermore, the FDA has interpreted the FDCA to permit using unapproved drugs in a "treatment-investigational setting" in the past. . . . The FDA, therefore, does not view every use of unapproved drugs as research, and nothing in the DoD Act [10 U.S.C. 980, requiring informed consent in DoD "research"¹ suggests that Congress intended the term to have such a broad meaning.

Doe v. Sullivan, 756 F. Supp. 12, 15-16 (D.D.C. 1991).

The Court of Appeals for the District of Columbia affirmed this decision in favor of the Government. The Court ruled:

While it is true that the FDA's prior interpretation of the words "not feasible" [in section 505(i) of the Act] focused on the subject's condition, the agency here has not reversed course. It has simply added a tightly circumscribed set of urgent circumstances in which the main rule of informed consent, with fidelity to the statute's terms, can be displaced- . . .

Doe v. Sullivan, 938 F.2d 1370, 1382 (D.C. Cir. 1991) (opinion by Judge Ruth Bader Ginsburg).

Not only was the regulation fully upheld by the courts, it is also consistent with ethical standards.. The primary issue in the ethical analysis is: Does the use of INDs by the military in the circumstances of the interim final rule constitute "research" in the context of ethical standards which prohibit nonconsensual research on human subjects? The Belmont Report² discussed the distinction between research and treatment:

² The Belmont Report, Ethical Principles and Guidelines for the Protection- of Human Subjects in Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, OPRR Reports, April 18, 1979.

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects in research. . . .

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a -reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge. . . .

When a clinician departs in *a* significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research.

The rule itself makes clear that the only purpose is treatment, and that there is no research purpose in the use of INDs in military combat exigencies. Again quoting the primary standard in the regulation:

The Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.

21 CFR § 50.23(d) (1). Nothing in the regulation even hints that the special authority is available if the military's purpose is to conduct research. One might suggest that the use of an IND for treatment purposes constitutes what the Belmont Report refers to as a departure from accepted practice. The same might be said for the common physician practice of off-label prescribing. But as the Belmont Report makes clear, this does not, as an ethical matter, convert a treatment purpose and effect into a research purpose or effect-

Another example in which a significant departure from standard clinical practice is not considered "research" is the

FDA's Accelerated Approval regulation, 21 CFR § 314.500, *et seq.* Under that regulation, an IND can be approved for marketing, and thus widespread treatment use, even if there is "uncertainty" as to clinical benefit, contingent on further post-marketing studies to follow* § 314.510. Post-marketing restrictions on distribution, labeling, and advertising may also be imposed pending additional evidence of safety and efficacy. §§ 314,520, 314.550, 314.560. However, during this process of conducting additional studies and collecting additional evidence, general uses of the drug are not considered to be research, nor are they subject to the protection of human subjects regulations. Additionally, FDA regulations also allow "treatment uses" of INDs, separate from ongoing research trials. 21 CFR § 312.34.

Once it is recognized that the use in a military combat exigency of drugs not yet approved by the FDA for general commercial marketing for the particular clinical indication is not "research" under law or ethical standards, the ethical justification for the mandatory use of protective drugs is not seriously debatable- Military members must make many sacrifices that in the civilian world would be considered intolerable. The Supreme Court has said: "The essence of military services is the subordination of the desires and interests of the individual to the needs of the service."³ Although military members do not give up their interest in not being nonconsensual research subjects, they must subordinate many individual interests to the needs of the military to complete successfully the mission. Among these is to accept preventive or therapeutic medical care that command authorities decide is necessary for the preservation of the fighting force.

Those who refuse to acknowledge legal and ethical justifications for the interim final rule rely essentially on a single semantical argument: that anything categorized by the FDA as an "investigational new drug" is an "experimental drug," which cannot be used for anything except "research." But this semantical argument is not based on any meaningful analysis of the Food, Drug and Cosmetic Act, FDA regulations, the Common Rule for the Protection of Human Subjects in Research, the Belmont Report on which the Common Rule was based, or any other

³ *Goldman v. Weinberger*, 475 U.S. 503, 507 (1986).

persuasive source. Perhaps most importantly, **the** superficial semantics do not attempt to address what the interim rule does and does not do, and how that relates to the legal and ethical standards applicable to research and treatment. The rule does not authorize a determination that informed consent is not feasible in connection with any military undertaking that fits the legal, ethical, or clinical description of "research-". The rule *allows* such a determination only when, based on the nature of the disease threat; the evidence of safety and efficacy of the drug to counteract that disease threat, and the lack of a satisfactory alternative, "withholding the treatment would be contrary to the best interests" of the military members.

6. Overall, notwithstanding some problems in carrying out the designed treatment protocols, the two uses made of the current rule *during* the Persian Gulf War support the rule's continuation.

Essentially, during the Persian Gulf War, DoD and FDA collaborated to do three significant things. One was to promulgate the rule authorizing a determination by the Commissioner that informed consent is not feasible in certain military combat exigencies. This rule was accepted by the courts and Congress and remains in effect today. The other two significant actions were the adoption, using the authority of the rule, of treatment protocols for the use of two IND products as medical countermeasures against certain suspected chemical or biological weapons threats. It is important to restate the facts with respect to these two actions.

With respect to the adoption of a treatment protocol for pyridostigmine bromide as a pretreatment antidote to nerve agent poisoning, the FDA thoroughly reviewed the issue through the Informed Consent Waiver Review Group (ICWRG), which included senior officials of the FDA, plus the Director of the Office for Protection from Research Risks (OPRR), HHS. In recommending approval of the DoD requested determination, these ICWRG members made the following findings:⁴

⁴ Memorandum to the Commissioner of Food and Drugs from Informed Consent Waiver Review Group, Subject: IND 23,509 - Pyridostigmine Bromide 30 mg Tablets - Action, January 8, 1991.

- o The use of pyridostigmine pretreatment, in conjunction with atropine and pralidoxime treatment, improved survival of animals exposed to soman. Limited human evidence suggests that the proposed dose of pyridostigmine will provide a level of enzyme inhibition in humans comparable to that achieved in animals which were protected from soman-induced mortality.
- o There is extensive experience in humans with myasthenia gravis using doses of pyridostigmine much greater than those proposed in this treatment protocol, and we have no specific safety concerns with the proposed military dose.
- o We agree with DoD that withholding treatment from an individual, based on personal preference *not* to receive the pretreatment with pyridostigmine, could jeopardize the health and safety of that individual or other military personnel in the event of a chemical attack.

Although the implementation of the approved treatment protocol for pyridostigmine was not problem free, *no* such implementation difficulties meaningfully call into question any of these determinations made by the ICWRG.

Similarly, the proposed treatment protocol for pentavalent botulinum toxoid vaccine also was thoroughly reviewed by the FDA. In adopting the staff recommendation, the Commissioner responded to DoD:⁵

Based on your assessment of the military operation, I find that there is no available satisfactory alternative therapy for the prevention of botulism, and I concur with your assessment that informed consent is not feasible and that withholding treatment would be contrary to the best interests of military personnel.

When the vaccine, which was in very limited supply, and the

⁵ Letter to Assistant Secretary of Defense (Health Affairs) from Commissioner of Food and Drugs, December 31, 1990.

approved treatment protocol reached the Gulf, the Central Command changed the protocol. It was modified (without notice to the Pentagon, as far as can be reconstructed, until after the fighting stopped) to permit members the choice of declining the vaccine. The Central Command Surgeon recently explained the change as being based on three primary factors:" 1) very limited vaccine supply; 2) the lack of intelligence reports that would have allowed prioritized use of the limited supply based on some judgments that certain personnel are more at risk than others; 3) Command concerns about rumors arising from a Stars and Stripes article reporting on allegations back home about requiring troops to take "experimental vaccines." Anecdotal reports leave somewhat unclear whether, in actual use throughout the theater of operations, the vaccine was uniformly administered in accordance with the Central Command's revised protocol or was sometimes given consistent with the original protocol.

The Central Command's revision to the protocol was a surprise to the DoD officials with whom the FDA was dealing. But.. in retrospect, it was quite proper to give the responsible military command the option to decide whether actual military circumstances unfolding in the theater of operations truly required the standardized use of the vaccine. Had intelligence reports changed or had the timetable for combat operations allowed for procurement of additional supplies, implementation of the original protocol might have been necessary after all. It was not unreasonable to give the Central Command that option. However, there was a breakdown in communications that prevented a common understanding among all involved officials. Had communications been better, the determination that informed consent was not feasible could have been contingent upon a final Command decision confirming the existence of, in the words of the rule, "special military combat (actual or threatened) circumstances" which "require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment."

⁶ Testimony of Brigadier General Robert Belihar before Presidential Advisory Committee on Gulf War veterans' Illnesses, Public Meeting, Kansas City, Missouri; January 12, 1996.

There were also implementation difficulties in connection with the uniform provision of information to personnel regarding pyridostigmine and the preservation of records in connection with botulinum toxoid vaccines. Efforts to carry out the planned distribution of revised information packets on pyridostigmine to the hundreds of thousands of troops deployed throughout the theater of operations were frustrated by the limited time between the FDA approval of the protocol January 8, 1991, and the beginning of Operation Desert Storm a couple of weeks later. With respect to record keeping and reporting on pyridostigmine, normal IND record keeping and reporting requirements had been waived by the FDA in recognition of the logistical realities and the reliance on self administration of the tablets. After the cessation of hostilities, several surveys were conducted, with results reported to the FDA. With regard to botulinum toxoid vaccine, appropriate record keeping and retention were frustrated by the Central Command's determination of the need for security classification regarding biological warfare defense vaccines (including both the licensed anthrax vaccine and the IND botulinum toxoid vaccine).

These several implementation problems establish the need for improvements, at least some of which have already been made in the implementation systems and procedures DoD relies upon in operational deployments. Perhaps most importantly, the treatment protocol development process needs to include people who are closer to the reality of the battlefield. However, none of these implementation difficulties during the Gulf War changes the fundamental fact that had the enemy used its apparent capability to deliver chemical or biological weapons, based on the available evidence of the safety and efficacy of these two IND products and the lack of an effective alternative treatment, the best medical countermeasures, as far as the medical establishment of the Government could determine, clearly included the treatment use of these products. And, in the context of the pending petition, nothing that happened during the Gulf War even remotely supports the argument that military personnel or the Government or the nation would be better off with the repeal of the current rule.

Some of the other criticisms of DoD and/or FDA actions during the Gulf War are without foundation. For example, evidence supporting the safety of pyridostigmine and botulinum toxoid was and still is quite solid. Pyridostigmine has been

used safely for more than 40 years as the principle treatment for myasthenia gravis at much higher doses over much longer periods than the regimen used in the Gulf. The drug does have side effects, but these are relatively mild. The evidence does not suggest a difference in safety between use by men and women. The recently published studies conducted by Moss and by Abou-Donia in cockroaches and chickens, respectively, used extraordinarily high dosages and routes of administration that differed from the route of administration used by Service members in the Gulf. Although providing potentially valuable preliminary scientific information, these data cannot be generalized to a human population. Similarly, decades of experience with botulinum toxoid vaccine provide a clear basis for confidence concerning safe use. The overwhelming weight of evidence continues to support the safety of these two IND products.

The efficacy of pyridostigmine has been questioned based on an Army study suggesting that it decreases the effectiveness of atropine and pralidoxime chloride against nerve agents sarin and vx. Pyridostigmine is used to counter soman poisoning based on evidence that it substantially enhances the effectiveness of the post exposure treatments against soman. Although it does decrease somewhat the effectiveness of atropine and pralidoxime against sarin and VX, the two treatments are so highly effective against sarin and VX, that any negative interaction of pyridostigmine and the nerve agent would be overwhelmed by the atropine/pralidoxime therapy. Thus, in predicted clinical outcome, pyridostigmine substantially improves medical protection against soman and does not affect medical protection against sarin and VX. In preparing medical countermeasures against the possibility of chemical weapons attack using any of these nerve agents, as was necessary in the Gulf War, predicted clinical outcome clearly calls for the use of pyridostigmine.⁷

⁷ The results of the sarin/VX study were reported to the FDA by the Army component responsible for administration of the pyridostigmine IND in full compliance with 21 CFR § 312.33. The study, conducted under a different Army command element, was unknown to the IND investigators until it was published. In any event, the results of the study do not affect the DoD or FDA conclusions regarding the evidence of efficacy of pyridostigmine for this clinical purpose.

7. Initiatives since the Gulf War, including current operations in Bosnia, have improved DoD's ability to implement medical countermeasures under the authority of the current rule, should that become necessary in the future.

Since the Gulf War, the Department has significantly improved its capability to monitor the health of military personnel deployed by the President to hazardous areas, such as the current Operation Joint Endeavor in Bosnia. As part of the "lessons learned" from the Gulf War, DoD has assigned a high priority to improved documentation of health information, including administration of medications and vaccines. A number of initiatives are in progress to enhance capabilities to manage medical information under field conditions. DoD has established a task force to address the issue of medical records in a military theater of operations. Records pertaining to the results of pre-and post-deployment health screening will be captured in an automated data base. DoD is expanding the automated Composite Health Care System (CHCS) medical record system to include a module for medical records of a deployed force- Attention is being directed toward developing a mechanism for computerizing medical data (including classified information, if and when it is needed) in the field to ensure standardized record keeping.

In May of 1994, DoD initiated an aggressive, clinical diagnostic plan, the Comprehensive Clinical Evaluation Program (CCEP) to offer intensive examinations to Gulf War veterans. The CCEP has provided an in-depth medical evaluation to eligible Service members concerned about their health. The CCEP provides an integrated system to evaluate the health status of service members who participate in deployments in the future. Modifications of the program will allow DoD to administer health questionnaires and conduct medical examinations of groups of deployed personnel, and collect the information through an automated process for entry into a centralized data base for subsequent analysis and interpretation.

Earlier this year, DoD released the *Medical Surveillance Plan for U-S- Ground Forces Deploying to Bosnia*, which has improved significantly the capability to monitor the health of the deployed force. The plan provided guidance, in conjunction

with directives from the Joint Chiefs of Staff, regarding implementation of a standardized medical surveillance program. The program expands capabilities in a number of areas including: health education, risk communication, standardized medical screening pre and post deployment, health hazards assessment, and in-theater medical surveillance. Upon return from the deployment, each service member will undergo health screening with the results annotated on standardized forms for entry into a central data base. In addition, DoD has established a telemedicine network within Bosnia that allows the projection of specialized diagnostic care and consultation forward to the patient.

As an aside, DoD efforts to provide effective countermeasures against medical risks in Bosnia include very careful planning regarding the use of two INDs. Tickborne Encephalitis (TBE) and Hemorrhagic Fever with Renal Syndrome (HFRS) are two infectious diseases which present serious potential health risks to U-S. forces operating in Bosnia. The Department through the Army Surgeon General filed INDs to use ribavirin as a treatment for HFRS and the Austrian TEE vaccine for immunization of military personnel, Medical staff have been notified that informed consent is required to administer these pharmaceuticals. In both of these cases, DoD determination that informed consent is feasible was based on a thorough analysis of the nature and extent of the health risk presented, the treatment context, the military situation, available alternatives, and, most importantly, the best interests of the members.

CONCLUSION.

For the reasons stated above, the Department of Defense urges that the petition be denied.