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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Dr.  
Rm. 1-23  
Rockville, MD 20857

To Whom It May Concern,

**Re: Docket No. 90N-0302**

I am providing comments in response to your request (62 FR 40996, July 31, 1997) concerning the "... advisability of revoking or amending the interim ~~final~~ rule that permitted the Commissioner of Food and Drugs to determine that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain situations related to military combat."

I am a retired U.S. Army officer who served initially as a commissioned officer in Armor. After taking my Ph.D. in psychology, I served in the Army Medical Service Corps (MS) as a research scientist and scientific manager. My assignments as an MS officer included about eight years at the U.S. Army Medical Research Institute of Chemical Defense. There I investigated pharmaceutical countermeasures-including pyridostigmine ~~bromide~~-to nerve agent exposure and the acute toxic mechanisms of nerve agents' action. Results of this work were published in peer reviewed scientific literature and presented at meetings of international scientific organizations (e.g., Society for Neuroscience). I also served in the Headquarters of the Department of the Army, Office of the Assistant Secretary of the Army for Research, Development and Acquisition, as the Technology Staff Officer for Chemical and Biological Defense.

*Summary perspective.* Title 21 CFR, *Food and Drugs*, together with Title 32 CFR, *National Defense*, should be revised to provide for the military use of FDA-regulated, investigational products (i.e., pharmaceuticals, biologics and devices) by explicit permission of The President of the United States. The CFR should define a process wherein The President would act on the recommendations of the Secretaries of Defense and of Health and Human Services. The Secretaries should be advised on the military need by the Chairman of the Joint Chiefs of Staff and on assessment of product benefit(s) and risk(s) by the Commissioner for Food and Drugs. The use of FDA-regulated investigational products in military operations, including operations short of war, should *not* be for product testing or other experimental purposes. Use of such products under those kinds of conditions should be for the humane purposes of preventing casualties,

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deaths and morbidity. Permission to use such products under those kinds of conditions is a policy, not a regulatory, decision. It is a decision that involves at least two, cabinet level Departments of the Executive Branch and it should be determined by The President.

#### **A. The Interim Rule**

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

The agency should revise the interim rule. Titles 21 and 32 CFR should be revised to provide a clear and efficient process for The President to permit the unlicensed and off-label use of otherwise FDA-regulated and investigational pharmaceuticals, biologics and devices during military operations. The Commissioner for Food and Drugs and the Food and Drug Administration (FDA) staff are routinely and predominately concerned with matters of medical product safety and efficacy. The predominate context for FDA regulation and decision making is the physician-patient relationship and the deliberate process of well controlled clinical testing. Requests for blanket or conditional waivers of FDA regulations places the staff and the Commissioner in an apparent conflict of interest. Just as The President has the authority and responsibility to mobilize and deploy United States armed forces, The President should have the responsibility and clear authority to permit unlicensed and off-label use of drugs, biologics and devices during military operations.

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

Yes. The circumstances were well defined by the Assistant Secretary of Defense for Health Affairs in his October 30, 1990 letter to the Assistant Secretary for Health of the Department of Health and Human Services (55 FR 528 14, December 21, 1990). In summary, there is ample legal precedent that requirements of military operations may supersede individual rights and freedoms that are routinely enjoyed in a civilian setting. Service men and women deserve the best protection that medical technology may provide to their health, safety and chances of surviving armed conflict, deployments and operations in hostile environments, exposure to endemic diseases, as well as effects of conventional weapons and weapons of mass destruction. The FDA and 21 CFR must not prevent such application of medical technology when scientific analyses of potential benefits outweigh product risks.

##### **(3) The interim rule is based on the premise that informed consent is not feasible in military combat exigencies.... Given the experience in the Gulf War, does this rationale still hold?**

Yes. The Gulf War experience is the basis for extensive lessons learned. It has been reported that individual service members attempted to not deploy to the Gulf and

cited their desire to not use investigational products as a reason. This experience validates the Defense Department's expressed concern about this matter.

A predominate lesson is that military operations are extremely demanding and dangerous, even when opposition forces are of very limited effectiveness and our casualty rates are low. Another lesson is that military commanders will likely not maintain clinical-investigation-quality record keeping during military operations. Service men and women will not uniformly comply with drug dosage schedules; compliance will likely be highly variable and be subject to rumor, individual beliefs and experience, and other factors while not being particularly susceptible to 'official-command-sources' of medical product information (e.g., informed consent).

There is no reason to believe that strict adherence to FDA investigational new drug (IND) regulations would have reduced the incidence of Gulf War Illness. While the cause(s) of the great human tragedy of Gulf War Illness remain undetermined, it unlikely that use of investigational products in strict adherence to FDA regulations would have altered the outcome. Regulatory compliance would have produced high quality clinical data. However, it is unlikely that IND protocols could have ethically provided sufficient control over environmental, operational, and other variables to have permitted even reliable correlations for guiding definitive research or clinical intervention.

Iraq's declarations to the United Nations Special Commission (UNSCOM) and evidence to date reinforce the very real threat to US and coalition forces from chemical and biological weapons in the Iraqi arsenal. These threats validate the need for provisions of the interim rule.

Finally, the Gulf War experience bolsters the Department of Defense (DoD) policy that appropriate vaccines should be used to immunize at-risk forces prior to their deployment. The DoD has demonstrated that it is capable of compliance with FDA regulatory requirements such as for medical and IND recording keeping, informed consent, protection of human subjects in testing and research, adverse event reporting and product recall. Completion of immunization schedules in a 'non-operational' environment improves compliance, reduces the incidence of unresolved issues associated with adverse events, and contributes to readiness and deployability of forces.

**(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?**

The concept of informed consent carries with it the right of the individual to terminate consent at any time and with no preconditions or explanations. Accordingly,

this line of reasoning is flawed. It would be reasonable to inform those volunteering for service in the armed forces of current policies and regulations regarding use of investigational products by military personnel. The “anticipatory consent” approach does not resolve the issue of preventing individuals from withholding informed consent as a way to avoid assignment or deployment to a high threat area.

**(5) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent . . . What would be the needed consent algorithm to make it valid and feasible?**

The line of reasoning reflected in these questions is flawed for the same reasons as in question 4 and it is impractical. Military service may extend for 30 years, or more. It is not possible to anticipate the investigational products that might be candidates for use over that timeframe. Over any period of individual service, DoD sponsored investigational products, as well as private sector investigational products supported by DoD funds, should be moving along toward FDA licensure. Thus, the numbers **and** specific investigational products that might be subject to “anticipatory consent” should be constantly changing. This variant of the informed consent approach does not resolve issues concerning DoD needs to assign and deploy forces.

**(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 President, as Chief Executive and Commander in Chief, should have clear authority and responsibility to permit the unlicensed and off-label use during military operations of medical materiel that is normally regulated by the FDA. It is likely that the Secretaries of Defense, Health and Human Services, and perhaps State might have conflicting views and opinions on the use of such products during military operations. The President should resolve such differences.

The Code of Federal Regulations should be revised to:

- Assign to The President of the United States the authority and responsibility to waive FDA regulations (31 CFR) and to permit, on a case-by-case basis, military commanders to order the use of medical products for humane purposes.

- Require the Secretary of Defense to advise The President of military needs and relative priorities for use of specific medical products requiring regulatory waivers and of case-by-case limitations or waivers that should be imposed as a condition of permission to use the products. The Secretary of Defense should be advised by the Chairman of the Joint Chiefs on the military needs and related operational considerations and by the

Secretaries of the Military Departments on product specific, medical and personnel policies (e.g., record keeping, command information programs, medical follow-up).

- Require the Secretary of Health and Human Services to advise The President, case-by-case, on product benefits and risks for the intended purpose, alternatives to the use of the product, recommended limitations on product use by military forces, and product specific and personnel policies. The Secretary of Health and Human Services should be advised by the Commissioner for Food and Drugs on a case-by-case assessment of benefits and risks, regulatory compliance and waiver concerns and recommendations, and the regulatory status (e.g., Phase II safety in how many subjects) of each product.

- Require the Chairman of the Joint Chiefs to advise the Secretary of Defense and the Secretary of Health and Human Services of military needs and relative priorities for use of medical products requiring regulatory waivers. The Chairman's advice should be:

- \* Provided at least every two years with preparation of the President's Budget, or more frequently as contingencies require and in sufficient time to allow effective consultation within the Executive Branch,

- . Based on validated and suspected threats to the health and safety of military forces with consideration given to the health of coalition forces and indigenous populations, and

- \* Developed in coordination with the Chiefs of Staff of the Military Services and with Defense Department institutional review boards (IRBs) that have been reviewing the products in question and those that are convened to review the specific scenarios in question. Advice of the Commissioner for Food and Drugs should be sought in developing the Chairman's recommendations.

- Require the Commissioner for Food and Drugs to advise the Secretary of Defense and the Secretary of Health and Human Services on a case-by-case assessment of benefits and risks, regulatory compliance and waiver concerns and recommendations, and the regulatory status of each product. The Commissioner should:

- \* Maintain the capability to convene scientific advisory committees on short notice and with clearances for working with national security information,

- \* Provide required advice at least every two years with preparation of the President's Budget, or more frequently as contingencies require and in sufficient time to allow effective consultation within the Executive Branch, and

- . Establish within the FDA Centers, points of contact for consultation on DoD product and program needs and issues.

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

The interim rule should be revised as outlined in response to A(6).

**(8) If the rule were to be repropounded:**

**(a) Should there be . . . without compromising military or national security?**

The DoD should not be required to use an independent IRB. Imposition of such a requirement would interfere with Presidential authority and responsibility, as Commander in Chief, to direct U.S. forces. An independent IRB with the necessary approval authorities could not be established without compromising responsibilities and authorities of the National Command Authority and the military chain of command; such an IRB would compromise national security.

**(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?**

Yes, the authority should be vested in The President.

**(c) Should the rule be more specific . . . or should FDA have wide latitude to make such determinations on a case-by-case basis?**

As outlined in response to A(6), the Commissioner should advise on a case-by-case basis.

**(d) Should additional measures be taken . . . what should these measures be?**

See the response to A(6). Military commanders must have the authority and responsibility to inform their forces. Imposition of the FDA into such military operational issues is wrong.

**(e) Should the rule address what constitutes adequate recordkeeping and adequate long term followup of individuals who receive investigational products? If so, in what way?**

See the response to A(6). The President, in consultation with the Secretary of Defense and the Secretary of Health and Human Services should make these determinations. It is important to recognize that use of the products in question is needed to conduct military operations while minimizing adverse health impacts. The main issues should not be about conducting tests during military operations. Furthermore, it would

be inappropriate for the Commissioner of the FDA to have such a direct influence on Defense budgets; long term medical followup of thousands of individuals could be very expensive.

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

See the response to A(5). As noted previously, the issue should not be treated as how to extend product testing procedures into military operations. The issue should be considered in the context of how to best employ off-label and unlicensed products to protect health and safety during military operations.

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

No. I don't believe that the use of these products should be considered as an issue of how best to conduct "product testing during military operations". Considerations of regulatory compliance must be secondary to, and not interfere with, the ability of military commanders and their forces to accomplish their missions.

**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?**

It is not ethical to conduct clinical testing with toxic **chemical** or biological agents unless there is certainty that effects are fully reversible. It is not scientifically possible to prove that agents are completely safe and their effects fully reversible, therefore such studies are not possible.

**C. If Products That May Be Used to Provide Potential Protection Against Toxic Chemical and Biological Agent Cannot be Ethically Tested in Humans, What Evidence Would Be Needed to Demonstrate Their Safety and Effectiveness?**

**(1) Should FDA identify the evidence needed to demonstrate safety and effectiveness of drugs . . . .**

Concerning safety, there is no reason that expanded Phase II safety trials and post-marketing surveillance could not be completed in non-deployed populations. Thus, product safety demonstrations should not present unique problems. FDA scientific advisory committees should be used to advise, on a case-by-case basis, on data (e.g., non-clinical or surrogate markers of efficacy) required to demonstrate efficacy. Additionally? post-marketing clinical data obtained from, for example, incidents involving accidental threat agent exposures by at risk workers or operating forces could contribute to the body of "substantial evidence" needed to demonstrate product efficacy. The main point is that,

as with other FDA regulated products, safety and efficacy of DOD-required medical products should be considered on a case-by-case basis and taking into account the intended indication and levels of medical supervision for product use.

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

There will likely continue to be investigational medical products of interest to the DoD. Natural evolution of disease threats and continuing development of technologies for manufacturing and delivering chemical and biological weapon threats as well as advances in technology for protection against these threats are likely to continue DoD interest in investigational medical products; the need for the interim rule will continue. If reliable markers for product efficacy and safety can substitute for clinical data, the pace of product licensure should increase and a greater percentage of licensed products reduces the potential frequency of reliance on the interim rule.

**(3) ... 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?**

Absolutely. The response to A(6) does not rule out the military use of investigational products in civilian populations. This contingency must be considered, both for DoD and for public health organizations.

Sincerely,



Daniel L. Rickett, Ph.D.