

MILITARY USE OF INVESTIGATIONAL MEDICAL PRODUCTS

STATEMENT

by

EDWARD MARTIN, M.D.

**PRINCIPAL ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS
(ACTING)**

before

COMMITTEE ON VETERANS' AFFAIRS

U.S. SENATE

MAY 06, 1994

**NOT FOR PUBLICATION
UNTIL RELEASED BY
COMMITTEE ON VETERANS' AFFAIRS
U.S. SENATE**

MILITARY USE OF INVESTIGATIONAL MEDICAL PRODUCTS

Mr. Chairman, distinguished Members of the Committee, I appreciate the opportunity to represent the Department of Defense before your Committee. Today, I would like to discuss the use of investigational drugs and biologics and the procedures we have in place which protect the health and welfare of our military personnel when such investigational products are used, both in peacetime and during military combat exigencies. Before I address that issue, however, I would like to draw a very clear distinction between the use of such products during the Persian Gulf War, and the human experiments involving mustard agents or Lewisite which were conducted almost half a century ago.

Human experiments involving mustard agents or Lewisite were conducted during World War II to ascertain the physiological effects of these compounds, to explore potential treatments, and to develop new measures of protection. The intention of these experiments was clearly **research**; to gain scientific information which was lacking on the effects of exposure to these chemical warfare agents. In addition, this research was conducted prior to any federal policy or regulation for protecting human research subjects.

On the other hand, investigational products were employed during the Persian Gulf War as prophylactic **treatments against biological and chemical warfare agents. This was not research but direct prevention and treatment.**

Referring to these products as "investigational" is in accordance with Food and Drug Administration (FDA) regulations and not a definitive statement regarding the scientific information available about the products. In the vernacular of the FDA, a drug is

"investigational" if it has not been approved by FDA for general commercial marketing for a particularly stated medical purpose. In the Persian Gulf War, DoD used two drugs that, although not approved by FDA for general commercial marketing for the particular medical purposes involved, were specifically allowed by FDA for the special military uses proposed by DoD. FDA allowed these uses because there was evidence they would be effective and no recognized alternative existed, and because FDA thought the use would be safe. The FDA also specifically allowed the use of these drugs in the military combat circumstances involved without the usual informed consent requirements required for investigational products. Withholding the use of these products would have been contrary to the best interests and possibly the lives of our military personnel.

I would now like to discuss the procedures which protect the health and welfare of our military personnel when investigational products are used, either in peacetime or during military combat exigencies.

Studies of new drug or vaccine products are conducted in animals to define dosages that may be safe and effective in humans. The findings from these studies are subsequently reviewed by the FDA as part of an Investigational New Drug (IND) application. Acceptance of the IND by the FDA then permits investigational products to be studied in humans. Under an IND, Phase I trials are conducted in humans to determine the safety of dosage and frequency of administration. Phase II trials are then conducted on a small "at-risk" population to demonstrate the efficacy of the drug or vaccine before application is made to the FDA to begin large scale Phase III trials, which would lead to approval or licensure. Approval or licensure by the FDA is based upon the results of well designed studies in humans which demonstrate efficacy and safety of the product.

For products designed to protect against biological or chemical warfare agents, a clear demonstration of efficacy would require deliberate exposure of humans to these highly lethal agents in order to determine effectiveness, such a protocol is clearly unethical in most cases and inappropriate. Thus, in the case of new products designed to protect or treat our troops against lethal biological or chemical warfare agents, the "normal" process of new drug approval is not feasible.

Under the Federal Food, Drug and Cosmetic Act, any use of an IND, whether for research purposes or for treatment purposes, must be preceded by obtaining informed consent from the subject or patient, unless it is "not feasible.". In all peacetime military applications, we believe strongly in informed consent and its ethical foundations. Furthermore, in peacetime, we readily agree to inform military personnel, as provided in FDA's regulations, that research is involved, that there may be risks or discomforts, that participation is voluntary and that one may refuse to participate without prejudice. However, during the existence of military combat exigencies, military personnel may be exposed to endemic diseases as well as chemical and biological warfare agents in a specified theater of operations. For some of these risks, the best preventive or therapeutic treatment calls for the use of products under IND protocols of the FDA. In situations of this kind, which the FDA interim regulations refer to as "a military combat exigency," informed consent procedures do not in our view apply. However, military personnel are to be given information concerning potential benefits or risks in taking the drugs. Under those regulations, a military combat exigency is one in which, in order to facilitate accomplishment of the military mission, preservation of the health of the individual and the safety of the other personnel, that a particular treatment must be provided to a specified group of military personnel, without regard to what might be any individuals' personal preference for no treatment or some alternative treatment. In such special circumstances,

the FDA Commissioner may approve a DoD request to waive normal informed consent procedures.

During the Persian Gulf War, two IND products, Botulinum toxoid and Pyridostigmine, were used to protect U.S. personnel against the potential use of biological and chemical warfare agents suspected to be in the Iraqi arsenal.

Pyridostigmine is a drug approved by the FDA since 1955 for use in the treatment of myasthenia gravis (MG), a neuromuscular disease. Pyridostigmine has been used safely in the treatment of MG at average daily doses of 600 mg. Pyridostigmine is also regarded as the product of choice by the Armies of NATO for the pre-treatment of organophosphate nerve agent intoxication and has been held in reserve by the DoD for that use since 1986. The dose used as a pretreatment in our military personnel during the Persian Gulf War was 15 percent of the average daily dose for MG (30 mg every 8 hrs - i.e. 90 mg daily).

Prior to its use in the Persian Gulf War, Botulinum toxoid had been used for more than 20 years in over 3000 individuals with over 10,000 vaccinations to prevent Botulism. The use of Botulinum toxoid is sponsored by the Center for Disease Control (CDC) in an IND to make this product available for medical use in persons at risk for occupational exposure to Botulism. The FDA has reviewed the annual reports of the administration of Botulinum toxoid to at-risk laboratory personnel and it continues to be used safely to protect laboratory workers.

Following the Persian Gulf War, the Assistant Secretary of Defense (Health Affairs) issued a policy memorandum which directed the Military Departments to document in the individual Service member's immunization record and health record

information regarding the receipt of Anthrax vaccine (a licensed vaccine) or Botulinum toxoid. The memorandum also required the Services to retain records regarding distribution of Pyridostigmine issued to various combat units. This information was considered classified due to order of battle and deployment of selected force units. The actual use of Pyridostigmine was accomplished by individual Service members themselves, and entry into medical records was not possible, since date, time frequency of use and dosage could not be clearly established.

In summary, Pyridostigmine and Botulinum toxoid were not used for experimental purposes in the Persian Gulf War and the military personnel who received these products were not experimental subjects. These products were used only after careful review both by a duly constituted human use review committee and the FDA. These products were used under the auspices of a treatment protocol, not an experimental protocol. With respect to both drugs, Dr. David Kessler, Commissioner of Food and Drugs, specifically found that in view of the risks associated with the potential use of biological or chemical warfare agents by Iraq and the lack of any alternative therapy, withhold these drugs "would be contrary to the best interests of military personnel".

The Department of Defense is committed to providing our military personnel with safe and efficacious medical products in peacetime and in combat. Regardless of the scenario, we will continue to furnish medical products to our Service men and women that will meet and respond to the world's evolving military requirements and biomedical technologies.

I want to thank you, Mr. Chairman, and the Members of this Committee for your interest in these issues, but more importantly for your concern for the health of Service members and Veterans.