THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

DEC 28 1990

David A. Kessler, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Doctor Kessler:

Under the provisions of 21 CFR 50.23(d)(1), as published in the Federal Register of December 21, 1990, I request a determination that obtaining informed consent is not feasible for pentavalent botulinum toxoid (ABCDE), BB-IND 3723, because of military combat exigencies in Operation Desert Shield. This determination would apply to the use of this drug by American military personnel at risk of exposure to botulinum toxins employed as biological warfare agents by enemy forces.

As summarized in enclosure 1 and supported by documentation in the IND file, available evidence supports the safety and effectiveness of pentavalent botulinum toxoid (ABCDE) for this purpose. The fatality rate among unvaccinated personnel exposed to botulinum toxins would be very high and many casualties would be expected. In such a situation, service members who became casualties would also pose a liability to their unit mission and the overall safety and well being of the other members of the unit. Pentavalent botulinum toxoid (ABCDE) is currently the only prophylactic measure available to persons who are exposed to botulinum toxins. During Operation Desert Shield, informed consent prior to vaccination with pentavalent botulinum toxoid (ABCDE) is neither feasible nor prudent for the foregoing reasons. The recommedation for use of pentavalent botulinum toxoid (ABCDE) without informed consent has been concurred in by a duly constituted institutional review board (enclosure 2).

Your prompt attention to this request is appreciated. A copy of this letter is being filed as an amendment to BB-IND 3723. Should you need further information concerning this request, please contact

#69

Lieutenant Colonel Gregory P. Berezuk, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, Maryland, 21702-5012, telephone (301) 663-2165.

Sincerely,

Signed

Enrique Mendez, Jr., M.D.

Enclosures

Copies Furnished:

Director
Center for Biologics Evaluation and Research
Division of Biological Investigational
New Drugs (HFB-230)
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892

Office of Health Affairs (HFY-1)
ATTN: Dr. Nightingale
Room 14-95
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

JUSTIFICATION FOR WAIVER OF INFORMED CONSENT FOR AN INVESTIGATIONAL NEW DRUG BECAUSE OF MILITARY COMBAT EXIGENCIES

1. IND

Administration of Pentavalent (ABCDE) Botulinum Toxoid IND # 3723, Protocol Title: Administration of Pentavalent Botulism Toxoid to At-Risk Individuals During.

2. INTENDED USE.

Pentavalent (ABCDE) Botulinum Toxoid is intended as a prophylactic treatment in the prevention of botulinum toxin poisoning (Botulism) for service members involved in Operation Desert Shield who are at risk of exposure. A team of specially trained personnel will be sent with the vaccine to train medical personnel responsible for the vaccination procedures. This vaccine will be administered by qualified medical personnel specially trained in the administration of Pentavalent (ABCDE) botulinum toxoid. It is envisioned that the Pentavalent Botulinum toxoid will be administered either in medical facilities prior to deployment and/or within the area of operation. The method of administration is described in the Informational Brochure (Attachment 1).

3. Safety of the drug.

Since 1970, almost 10,000 injections of the toxoid have been administered to recipients who were subsequently observed for adverse reactions. The rate of moderate and severe local reactions was 5.8% for the initial series. The rate of systemic reaction was very low (3.0 %) consisting of mild symptoms such as fever, tiredness, headache, and muscle pain. These systemic reactions were usually concurrent with the local reaction. This vaccine has successfully protected laboratory workers for 25 years with only minor reactogenicity and no fatalities.

4. Effectiveness of the drug.

Current available evidence has shown that Pentavalent (ABCDE) Botulinum Toxoid is immunogenic in humans in sufficient quantities after the third dose. Humans have neutralizing antibodies to the serotypes present in the vaccine and these levels are considered protective against the BW threat. Although no humans have been challenged with Botulism toxin an extrapolation of the animal data available suggests that humans are protected. In experiments with the toxoid, 30 persons were immunized on a 0-2-12 week interval. Antitoxin was detectable in 80% of the volunteers two weeks after the third dose of the initial series. This vaccine has successfully protected laboratory workers handling the deadly botulinum toxins for the

past 25 years. (for additional details see BB-IND-161 and BB-IND 3723).

5. Military combat exigency

Pentavalent (ABCDE) Botulinum toxoid will be administered to all service members in an area of operation who are considered at risk to imminent exposure to botulinal toxins. Pentavalent (ABCDE) Botulinum toxoid will be administered to accomplish the military mission and preserve the health of each service member and the safety of the unit of military personnel threatened. This will be necessary without regard to what might be any individual's personal preference for no vaccination or an alternative treatment, should any individual have such a personal preference.

6. Consideration of alternatives.

There is no alternative prophylactic protection against the effects of Botulinum Toxins (ABCDE).

7. Nature of the disease or condition involved.

Botulism is a life threatening disease.

8. Best interests of military personnel.

Under the circumstances presented, withholding Pentavalent Botulinum Toxoid (ABCDE) from any individual service member threatened with Botulism toxin intoxication would be contrary to the best interests of that individual.

9. Information to be provided to recipients of the IND.

Recipients of Pentavalent (ABCDE) Botulinum Toxoid will receive information from the medical personnel administering the vaccination concerning the drug. This information will include: a. the fact that Pentavalent Botulinum toxoid (ABCDE) is an investigational new drug (IND), b. minor to moderate reactions to the vaccine are possible and these should be reported to medical personnel, c. Pentavalent Botulinum toxoid is the only prophylactic treatment (prevention) for Botulism. Additionally, personnel receiving the toxoid will remain in the immediate area for 30 minutes after receiving each dose to monitor immediate adverse effects. A 48 hour post vaccine arm examination will be requested. Vaccinees will be informed that they are to report any adverse local and/or systemic reactions that occur within one week after administration of the vaccine. (See BB-IND 3723 Informational Brochure, Attachment 1).

10. Institutional Review Board approval.

A duly constituted and designated institutional review board carefully considered the use of Pentavalent (ABCDE) Botulinum

Toxoid without informed consent at its meeting of October 17, 1990. A copy of the pertinent portion of the minutes of the meeting is enclosed (Enclosure 2).

11. Manufacturing Information.

Pentavalent (ABCDE) Botulinium toxoid is manufactured by the Michigan Department of Public Health. The supplier is the U.S. Army Research and Development Command, Ft. Detrick, Maryland, 21702. All manufacturing information concerning the production of Pentavalent (ABCDE) Botulinum Toxoid is contained in Investigational New Drug Applications BB-IND-161 and BB-IND 3723. BB-IND-3723 contains authorization from the CDC for the Department of the Army to cross-reference BB-IND 161. A letter from the Center for Disease Control authorizing the Office of the Surgeon General to cross reference all aspects of BB-IND-161, including manufacturing information is enclosed (Attachment 2).

INFORMATIONAL BROCHURE
PENTAVALENT (ABCDE) BOTULINUM TOXOID

COMPOSITION

PENTAVALENT (ABCDE) BOTULINUM TOXOID ALUMINUM PHOSPHATE ADSORBED is a combination of aluminum Phosphate-adsorbed toxoid derived from formalin-inactivated, Partially Purified types A,B,C, D, and E botulinum toxins. Each vial contains 0.022% formaldehyde and 1:10,000 thimerosal as a preservative. The currently distributed toxoid is manufactured by the Michigan Department of Public Health.

Administration and Dosage

SHAKE WELL before withdrawing each dose. Administer 0.5 ml of vaccine via deep subcutaneous injection; do not inject intracutaneously or into superficial structures. Vaccinees will remain in the area where the vaccine is administered for no less than 30 minutes after receiving each dose to monitor immediate adverse effects. A 48 hour post vaccine arm examination is desirable following each inoculation. Vaccinees should be informed that they are to report any adverse local and/or systemic reaction that occurs within one week subsequent to the administration of the vaccine. The first injection is represented by week 0. There is a 2 week interval between the first and second injection and a 12 week interval between the first and third injection.

Initial Vaccination Series: 0.5 ml. deep subcutaneously at 0-2-12 weeks.

First Booster: 0.5 ml. deep subcutaneously 12 months after the first injection of the initial series.

Receipt of each vaccine dose will be recorded in the individuals permanent vaccine file. Additionally, a subset of approx. 100 vaccinees receiving each vaccine sublot will be prospectively identified for monitoring by a postcard-based questionaire.

PRECAUTIONS

1. Botulinum toxoid is not a licensed product and is distributed as an Investigational New Drug (IND) in accordance with the requirements of the U.S. Food and Drug Administration (FDA). It must be administered under the supervision of qualified medical personnel.

2. The toxoid should be administered only to healthy men and women between the ages of 18 and 65 years, since investigations have been conducted exclusively in that population.

3. Pregnancy. The effects of administration of the toxoid during pregnancy have not been established. Data are not available on the safety of pentavalent botulinum toxoid for the developing fetus. There should be no risk to the fetus from the product itself because the toxoid contains only inactivated protein. However, a theoretical risk from severe allergic reaction or anaphylaxis does exist. The incidence of severe systemic reactions has been extremely low (< < 1%) in previous recipients (male and female) of this vaccine. In contrast, the risk to the developing fetus of botulism is probably considerable. The toxoid should be given only to those persons deemed "at risk" to exposure of Botulinum toxin. Therefore, in a high-risk situation, pregnancy should not be considered a contraindication for vaccination with botulinum pentavalent toxoid.

4. No one should be administered a second or subsequent booster immunization unless laboratory test have shown antitoxin type B and or E to be below a satisfactory level.

IMMUNOGENICITY

Experience with pentavalent botulinum toxoid has shown that: (A) it is effective in protecting animals against intraperitoneal challenge with toxins of types A,B,C,D, and E of Clostridium botulinum. (B) the serum antitoxin levels in animals as determined by mouse protection tests correlate with protective activity , and (C) the toxoid introduced into man produces levels of antitoxin thought to be protective as judged by extrapolation of data derived from animal experiments.

In experiments with the original lot of toxoid (2,3), 30 persons were immunized on a 0-2-12 week schedule. Antitoxin titers were detectable for all 5 types of toxin in about 80% of the volunteers 2 weeks after the third dose of the initial series. Only a small percentage had measurable titers by one year, just before the boosters were given. Eight weeks after the boosters, 100% of the recipients had measurable titers to all 5 types.

Since initiating the requirement for determining antitoxin levels in recipients due for boosters, the immunogenicity of the toxoid in humans has been reaffirmed. (Only types A, B and/or E antitoxins are routinely assessed.) While the antitoxin titers attained after the 3rd shot of the initial series are likely to decline in a matter of a few months, those established after the first booster are relatively stable and generally persist above the detectable level for at least 2 years. A titer of 1:16 (0.15-0.30 IU antitoxin per ml.) for either B or E antitoxin is considered satisfactory for deferring a booster for 2 more years. After evaluating sera from 185 recipients taken in 1986, 1987 and 1988 who were due for booster, 81 (43%) were able to postpone them.

The immunogenicities in humans of the two new lots of toxoid (Lots A-2 and B-1) and of the original lot (181) were assessed by the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) and the results are available for comparison (1). The type B antitoxin levels attained after the 3rd injection of the new lots were significantly higher for the original lot.

In 1988 USAMRIID evaluated immunized individuals for neutralizing antibodies to type A & B botulinum toxins. After the Primary series 91% had a type A titer ≥ 0.08 IU/ml, and 78% type B titer ≥ 0.02 IU/ml. After the first booster all individuals tested had a demonstrable titer for type A & B (4).

ATTACHMENT 1

REACTIONS

Since 1970, almost 10,000 injections of the toxoid have been administered to recipients who were subsequently observed for adverse reactions. The rate of moderate and severe local reactions was 5.8% for the initial series of shots and 10.7% for booster shots (Table I). In addition, there was a low incidence of systemic reactions (3.0%) for both the initial series and the booster shots. The systemic reaction were generally mild consisting of fever, tiredness, headache, and muscle pain. Systemic reactions were often concurrent with local reactions. Moderate or severe systemic reactions and severe local reactions are not anticipated. Because of the documented increase in reactions, new lots of toxoid were manufactured in 1971, but distribution of the original lot was continued until 1981. A recent report on a very limited study on the reactogenicity of the new lots of toxoid indicated that they are probably no less reactogenic than the previous lot (1). Noting the higher incidence of local reactions following subsequent yearly boosters than following initial series shots, it was deemed advisable to evaluate the need for boosters by determining antitoxin levels and to boost only when necessary. This approach revealed that boosters subsequent to the first one are not necessary more frequently than at 2 year intervals and that many of these boosters can be avoided. Prior to 1974, yearly boosters were routinely given. Moderate local reactions include erythema, edema and induration. All such reactions reach a peak in 24 hours, then gradually subside and should be gone at 48 or at the most 72 hours. When a moderate local reaction occurs, reduction of the dose of each subsequent injections to 0.25 ml has been shown to alleviate the reaction without impairing the antitoxin response. Rarely, an individual may have a reaction characterized by a deep, painless, noninflammatory subcutaneous induration that may persist for 3 to 4 weeks. These rarely measure more than 2 to 3 centimeters in diameter and are absorbed without residue.

SUPPLIER

The toxoid is supplied by the U.S. Army Medical Research and Development Command (USAMRDC), Ft Detrick, Frederick, Md. 21701. Inquiries for toxoid should be directed to:

U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)
ATTN: SGRD-UIM (LTC McKee)
Medical Division
Ft. Detrick, Md. 21702-5011
Telephone: 301-663-7655
-OR-
U.S. Army Medical Materiel Development Activity
Biological Systems Project Management Division
Product Manager
Pentavalent Botulinum Toxoid (ABCDE)
Division of Biologics
Ft. Detrick, Md. 21702
Telephone: 301-663-7661

REFERENCES

1. Anderson, J.M. and Lewis, G.E., Jr. Clinical Evaluation of Botulinum Toxoids. In Biomedical Aspects of Botulism. Academic Press, New York, pp. 233-246, 1981

2. Cardella, M.A. Botulinum Toxoids. In Botulism, Proceedings of a Symposium. PHS No. 999-FP-1, Public Health Service, Cincinnati, pp. 113-130, 1964.

3. Fleck, M. A., Cardella, M.A., and Gearinger, N.F. Studies on Immunity to Toxins of Clostridium botulinum. IX. Immunologic Response of Man to Purified Pentavalent A,B,C,D,E Botulinum Toxoid. J. Immunol. 967-702, 1963.

4. Siegel, L.S., Human Immune Response to Botulinum Pentavalent (ABCDE) Toxoid Determined by a Neutralization Test and by an Enzyme-Linked Immunosorbent Assay. J. Clin. Micro. 26: 2351-2356, 1988.

Table I
Local Reactions to Botulinum Pentavalent (ABCDE) Toxoid ('70-88)
Number of Reactions (%)

Injection Number Injections	None or Mild	Moderate	Severe*
1	2356	90	3
2	2199	153	4
3	1947	148	5
Subtotal	6500	391(5.6)	12(0.2)
Booster Injections			
1	1079	141	14
2	496	53	5
3	290	28	5
4	884	77	1
Unknown	11	2	0
Subtotal	2769	301	25
Subtotal %	(89.2)	(9.8)	(0.2)
Total	9267	692	37
Total %	(92.7)	(6.9)	(0.4)

Key

None = No Reactions
Mild = Erythema only; edema or induration which is measurable but 30 mm or less in any one diameter.
Severe = any reaction measuring more than 210 mm in any one diameter or any reaction accompanied by marked limitation or motion of the arm or marked axillary node tenderness.

* MODERATE AND SEVERE REACTIONS AS DEFINED BY THESE CRITERIA ARE NOT INCAPACITATING.

September 5, 1990

Subject: BB-IND 161 - Pentavalent Botulinum Toxoid

Director
Center for Biologics Evaluation and Research
Division of Biological Investigational New Drugs (HFB-230)
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892

Dear Sir:

We authorize the FDA to cross-reference our Investigational New Drug application BB-IND 161 when reviewing submissions for the same product from the Department of the Army, Office of the Surgeon General (OTSG).

We also authorize the Department of the Army, OTSG, to cross-reference BB-IND 161.

Sincerely,

Paul A. Blake, M.D., M.P.H.
Chief, Enteric Diseases Branch
Division of Bacterial and Mycotic Diseases
Center for Infectious Diseases

cc W. E. Brandt
J. Becher

PASS TO Lt Rosenberg

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

From Walt — 9 PAGES

Food and Drug Administration
Rockville MD 20857

December 31, 1990

Enrique Mendez, Jr., M.D.
Assistant Secretary for Defense, Health Affairs
Department of Defense
Washington, D.C. 20301-1220

Dear Dr. Mendez:

I have received your request, dated December 28, 1990, and submitted pursuant to 21 CFR 50.23(d), for a determination that obtaining informed consent is not feasible for the investigational agent pentavalent botulinum toxoid vaccine.

In reviewing the justification for your request, I have considered the pertinent factors set forth in the regulation. Based upon 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.

My determinations expire one year from the date of this letter, or when the Department of Defense informs the Commissioner of Food and Drugs that the specific military operation creating the need for the investigational agent has ended, whichever is earlier.

Sincerely,

David A. Kessler, M.D.
Commissioner of Food and Drugs

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

DEC 28 1990

HEALTH AFFAIRS

David A. Kessler, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Doctor Kessler:

Under the provisions of 21 CFR 50.23(d)(1) (as published in the Federal Register of December 21, 1990), I request a determination that obtaining informed consent is not feasible for pyridostigmine bromide 30mg tablets, IND 23,509, because of military combat exigencies in Operation Desert Shield. This determination would apply to the use of this drug by American military personnel at risk of attack with chemical weapons involving organophosphorous nerve agents.

As summarized in enclosure 1 and supported by documentation in the IND file, available evidence supports the safety and effectiveness of pyridostigmine pretreatment, in conjunction with other drugs as treatments, for this purpose. If threatened with these chemical weapons, the interests of individual service personnel and the overall needs of the military service will require that pyridostigmine be used by all threatened personnel. No satisfactory alternative regimen involving investigational or approved drug products is available to deal with these life-threatening weapons. Under these circumstances, withholding pyridostigmine from any threatened individual would be contrary to that individual's best interests. The recommendation for use of pyridostigmine without informed consent has been concurred in by a duly constituted institutional review board, enclosure 2.

Your prompt attention to this request is appreciated. A copy of this request is being filed as an amendment to IND 23,509. Should you need further information concerning this request, please contact

Lieutenant Colonel Gregory P. Berezuk, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, Maryland, 21702-5012, telephone (301) 663-2165.

Sincerely,

Signed

Enrique Mendez, Jr., M.D.

Enclosures

Copies Furnished:

Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Office of Health Affairs (HFY-1)
ATTN: Dr. Nightingale
Room 14-95
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

1/4/91

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date JAN 8 1991

From Informed Consent Waiver Review Group (ICWRG)

Subject IND 23,509 - Pyridostigmine Bromide 30 mg Tablets - ACTION

To Commissioner of Food and Drugs

The Assistant Secretary of Defense (Health Affairs) submitted a request to you, dated December 28, 1990, for a determination that obtaining informed consent for the aforementioned investigational agent is not feasible because of the military combat exigencies in Operation Desert Shield (Tab 1). The Department of Defense (DOD) provided the information set forth in 21 CFR 50.23(d)(1).

The Department of Defense believes that there is a serious threat that Iraq will use chemical or biological weapons against American military personnel in the Persian Gulf. In light of this threat, DOD believes that it is their responsibility to provide American military personnel the best available medical care and other defenses against such weapons. Because these weapons can be lethal, it is essential that each individual exposed to them receive the best medical treatment available, including pretreatment with pyridostigmine bromide 30 mg tablets, to enhance that individual's chances of survival. DOD further emphasizes that the protection of each individual is also important to other military personnel whose safety depends on the integrity of the unit and the ability of each person to perform his or her assigned role. If individuals could choose not to receive pyridostigmine, they would, therefore, not only be jeopardizing their own life but also the lives of others in their units. Finally, the success of the military goals of Operation Desert Shield depends in large part on preserving the health and capability of the American military force. For these reasons, DOD has concluded that special military combat circumstances exist in which it is not feasible to obtain informed consent for the use of pyridostigmine bromide.

Background

Under the provisions of 21 CFR 50.23(d), published in the FEDERAL REGISTER on December 21, 1990, the Commissioner may determine that informed consent is not feasible when the physician responsible for the medical care of the military personnel and the investigator named in the IND provide appropriate justification and the Commissioner finds that withholding treatment would be contrary to the best interests of military personnel and there is no satisfactory alternative therapy (Tab 2).

A meeting of the Informed Consent Waiver Review Group (ICWRG) was convened on January 4, 1991, pursuant to the agency's procedure to review requests from the Department of Defense. The ICWRG consists of FDA representatives and the Director, Office for Protection from Research Risks (OPRR), HHS. Representatives of the Department of Defense were present at FDA's request to serve as a resource to the ICWRG.

Informed Consent Waiver Review: Pyridostigmine Bromide 30 mg Tablets

Safety and Effectiveness for the Intended Use:

The Center for Drug Evaluation and Research (CDER) has reviewed the IND 23,509 submitted by DOD for use of pyridostigmine in treating military personnel who are at risk of exposure to organophosphorus nerve agents. In addition, two classified documents submitted by DOD were examined. Relevant portions of IND 23,509, including the clinical protocol, are at Tab 3.

There are pertinent safety data in both animals and humans. Pyridostigmine will be used by the military at a daily dose of 90 mg, only 15% of the typical human daily dose of 600 mg used in the treatment of myasthenia gravis. Efficacy data are based wholly on studies in animals. Pyridostigmine 1.2 mg/kg (twice the human dose proposed in Operation Desert Shield) afforded very significant protection (over 20 fold) against soman-induced mortality in monkeys when used with a standard oxime-atropine antidote. Extrapolation of this effect to humans is based on selection of a dose that achieves a 20% inhibition of blood acetylcholinesterase (AChE) in humans, which is the degree of inhibition attained in the protected monkeys. The CDER review, dated January 2, 1991, is at Tab 4,

document 1.

DOD has made a determination, based on several years of civilian and military research, that pretreatment with pyridostigmine 30 mg tablets three times daily, in combination with atropine and pralidoxime, given after exposure, will constitute effective pretreatment of organophosphorus nerve agent exposure.

The CDER concludes, based on its review of the safety and effectiveness data, that pyridostigmine 30 mg tablets, in conjunction with atropine and pralidoxime, is the only potentially useful pretreatment to reduce mortality after exposure to chemical weapons involving organophosphorus nerve agents (Tab 4, document 2). There is no ethical means of carrying out a relevant human efficacy study. In the absence of human data, there is less than full certainty as to pyridostigmine's effectiveness in man at the recommended dose, but the extrapolation from rhesus monkey and other animal data is not unreasonable, and pyridostigmine has been protective to at least some extent in other species studied.

Context of Drug Administration

The request for waiver from DOD refers to the use of pyridostigmine during potential hostilities associated with Operation Desert Shield. Operation Desert Shield is the name of the military effort mounted in response to the Iraqi invasion of Kuwait in August 1990. There are numerous press accounts that describe Iraq's use of organophosphorus nerve agents as offensive weapons during the conflict with Iran. The DOD believes that there is a serious threat that Iraq will use chemical and biological agents.

The instructions for use contained in IND 23,509 describe how military personnel will self administer the tablets in conjunction with other approved products, for the treatment of exposure to organophosphorus nerve agents when the risk of imminent attack is high (Tab 1, attachment 3, page 2-16). The drug will be taken under the order of the corps/division/wing commander. After three days of pre-treatment, the commander will review the decision to continue treatment for the full twenty-one doses.

Measures available to those at risk of nerve agent exposure consist primarily of barrier protections such as chemical protective masks, battle dress overgarments, chemical agent detection systems and decontamination kits, and secondarily of antidote therapy that consists of pyridostigmine pretreatment, a 30 mg tablet every eight hours, when the threat of exposure to the nerve agent exists, and the administration of atropine and pralidoxime by injection immediately upon exposure to nerve agent. This three drug treatment is expected to enhance the likelihood that exposed military personnel will continue to breathe spontaneously and not die of respiratory arrest.

The Nature of Organophosphorus Poisoning

Nerve agents are classified as anticholinesterase compounds because they inhibit the enzyme acetylcholinesterase (AChE). The inhibition of AChE has been considered to be the initiating factor in nerve agent toxicity. The nerve agents combine with AChE to prevent its normal function of terminating acetylcholine's (ACh) actions at synaptic, particularly neuromuscular, junctions.

Nerve agents include tabun (GA), sarin (GB), soman (GD), and VX. The G-agents, developed in Germany from 1938 - 1944, are all highly toxic organophosphorus compounds that are liquids at room temperature and that readily vaporize under normal atmospheric conditions.

The human lethal concentration per unit time (LCt_{50}) for sarin is estimated to be 25 mg/min/m^2. This means that approximately 50% of an unprotected group would die following one minute's inhalation of air which contained sarin 25 mg/m^3. The comparative toxicity of these products can be ranked as follows: VX > soman > sarin > tabun.

Sequelae from exposure to chemical weapons involving organophosphorus nerve gas agents are dependent on many factors, including any actions taken to avoid or reduce the magnitude and impact of casualty production. Under certain circumstances, incapacitation and death may occur.

Nature of the Information Distributed to Recipients

The ICWRG has reviewed the information from DOD that is to be

given to all military personnel at risk for exposure to organophosphorus nerve agents. The information is contained in the field manual publication FM-265, which is made available to the recipients (Tab 5, document 1), and the training manual 90-4, for health care professionals (Tab 5, document 2). The ICWRG was concerned that the text of the field manual clearly implies that there is evidence of effectiveness in humans, and requested that additional information be provided to all potential recipients of the product. A draft information sheet provided by DOD following the ICWRG meeting has been modified by DOD to reflect our recommendations (Tab 5, document 3). The additional information contained in the document will be provided immediately to all newly trained persons and in a timely way to all other individuals. Also, DOD agreed to modify the field manual at the earliest opportunity to remove any implications that there are human studies that show effectiveness of pyridostigmine pretreatment.

Expiration Date

If you determine that obtaining informed consent is not feasible, the determination will be in effect either for a period of one year or until DOD notifies FDA that the exigencies for which it needed the determination no longer exist, whichever is earlier.

ICWRG Recommendation

The ICWRG recommends that you approve the DOD request and determine that informed consent is not feasible. Our recommendation is based on the following:

- 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.

- 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.

- 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.

- We agree with DOD that there is no available satisfactory alternative pre-treatment for organophosphorus nerve agent exposure.

- We have reviewed the field manual FM 8-285, and the USAMRICD technical memorandum 90-4 that will be distributed to the health care professionals responsible for the education and treatment of military personnel, and other training material that will be made available to physicians and unit commanders about organophosphorus nerve agents. DOD agreed to modify the field manual at the earliest opportunity to remove any implication that there are human studies that show effectiveness of pyridostigmine pretreatment. We have also reviewed the document Countermeasures Against Chemical Warfare Agents: Additional Information on Pyridostigmine, dated January 8, 1991, that will be used to update military personnel about protections against organophosphorus nerve agent exposure. We conclude that with the dissemination of this information in that document and DOD's commitment to update training materials, the essential information on risks and benefits of receiving pyridostigmine tablets, the risks associated with not receiving pyridostigmine, and the nature of the disease has been provided.

- The Commissioner received a statement from DOD that the proposed protocol for the use of pyridostigmine without informed consent has been reviewed by a duly constituted IRB. The IRB concluded that the waiver is appropriate.

- The Department of Defense request meets the requirements of 21 CFR 50.23(d).

Director, ODE I, CDER

Associate Director for
Research and Regulatory
Coordination, CBER

Director, ODE II, CDER

Chief Counsel, FDA

Associate Commissioner
for Health Affairs

Director, Office for
Protection from Research
Risks, HHS

Attachments:

Tab 1 - Letter from the Assistant Secretary of Defense, Health Affairs, with attachments, requesting a waiver of informed consent, dated December 28, 1990.

Tab 2 - Interim Rule Informed Consent for Human Drugs and Biologics; Determination That Informed Consent Is Not Feasible, dated December 21, 1990.

Tab 3 - 1. WR 250,710 Investigational New Drug Summary, Pyridostigmine Bromide, undated.

2. IND #23,509 Protocol Amendment, dated January 2, 1991.

Tab 4 - 1. CDER Review of Department of the Army's Request for Waiver of Informed Consent For Use of Pyridostigmine 30 mg under IND 23,509.

2. Memorandum from Director, CDER to ICWRG, dated January 8, 1991.

Tab 5 - 1. Field Manual "Treatments of Chemical Agent Casualties and Conventional Military Chemical Injuries, dated February 1990.

2. USAMRICD Technical Memorandum 90-4 Pyridostigmine, with cover memorandum dated November 29, 1990.

3. Countermeasures Against Chemical Warfare Agents: Additional Information on Pyridostigmine, dated January 8, 1991.

DECISION:

Concur _____ Non-Concur _____ Date Jan 8, 199

David A. Kessler, M.D.
Commissioner of Food and Drugs

9100 5915

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D.C. 20301-1200

HEALTH AFFAIRS

22 JUL 1991

MEMORANDUM FOR ASSISTANT SECRETARY OF DEFENSE (FM&P)
ASSISTANT SECRETARY OF DEFENSE (RA)
ASSISTANT SECRETARY OF THE ARMY (M&RA)
ASSISTANT SECRETARY OF THE NAVY (M&RA)
ASSISTANT SECRETARY OF THE AIR FORCE (MRAI&E)

SUBJECT: Recording of Vaccinations Received in Operation Desert Shield/Desert Storm in the Medical Immunization Record (SF 601)

During the Persian Gulf operation, selected units of the Armed Forces received prophylactic vaccinations of anthrax vaccine or botulinum toxoid vaccine. To ensure operational security, the employment of these vaccines and the selected units immunized were considered classified information. Individuals who were so immunized had this information recorded on various documents, rosters, medical immunization record (SF 601), or International Certificate of Vaccination (PHS 731). For anthrax vaccine, medical personnel may have recorded the information as "Anthrax", "A vaccination", "A-Vacc", "A-Vax" or something similar. For the botulinum toxoid, medical personnel may have recorded the information as "Botulinum", "Bot-Tox", "B vaccination", "B-Vacc", "B-Vax", or something similar.

For continuity of medical records and to ensure the accuracy of medical care, all active duty and reserve units so affected must assure that documentation of vaccination is entered into the Medical Immunization Record SF 601 in the accepted medical format as "Anthrax Vaccine" and "Botulinum Toxoid." This action should be initiated while records and units so affected are still accessible. The Services should ensure that unit rosters or unit immunization logs are retained for purposes of epidemiological tracking. Documentation of these immunizations into the individual's medical record is considered unclassified information; however, the original records and documents used in identifying units and personnel immunized during Operations Desert Shield and Desert Storm are still considered classified information and should be treated appropriately.

I request that the Assistant Secretaries of the Military Departments report to me within six months of issuance of this memorandum the status of actions taken, or upon completion of the above requirement, whichever may occur earliest. Please identify

any difficulties which may be encountered in unit or personnel identification and any decisions taken to preserve available records.

Enrique Mendez, Jr., M.D.

Copies to:
Surgeons General

I request that the Assistant Secretaries of the Military Departments report to me within six months of the date of this memorandum the status of actions taken, or the completion of the above requirement, whichever may occur [illegible] please identify