APPENDIX EE

JULY 22, 1997

LETTER FROM DEPARTMENT OF HEALTH AND HUMAN SERVICES TO EDWARD D. MARTIN, M.D., ACTING ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 22, 1997

Edward D. Martin, M.D.
Acting Assistant Secretary of Defense for Health Affairs
The Pentagon
Room 3E-346
Washington, D.C. 20301-1200

Dear Dr. Martin:

The Food and Drug Administration (FDA) has been reviewing the Department of Defense's (DOD) use of investigational products and the waiver of informed consent under the December 21, 1990, Interim Rule entitled "Informed Consent for Human Drugs and Biologics; Determination that Informed Consent is not Feasible" during the Persian Gulf War. These issues have also been reviewed by the Presidential Advisory Committee on Gulf War Veterans' Illnesses, the General Accounting Office (GAO), and various Congressional Committees.

We also have recently received and reviewed a copy of unclassified excerpts from the April 15, 1997, GAO report concerning DOD's efforts to develop a vaccine immunization program for biological warfare defense, which, in part, examined the Department's use of a tick-borne encephalitis (TBE) vaccine in Bosnia under an investigational new drug application (IND); a copy of the DOD's response to the GAO report, which does not dispute the GAO findings discussed below; and a copy of the May 13, 1997, GAO report on the adequacy of DOD medical surveillance for deployments since the Gulf War. In addition, we have reviewed the results of an FDA inspection related to the Bosnian TBE vaccine study conducted at Ft. Detrick by Ms. Rebecca Olin on June 3-6, 1997. FDA conducted this inspection, in part, in follow up to findings presented in the April 15, 1997, GAO report that come under FDA's jurisdiction.

Based on our review and evaluation of the information included in the FDA inspection and GAO reports, and our ongoing evaluation of the use of investigational products in the Persian Gulf, we have identified significant deviations from federal regulations published in Title 21, Code of Federal Regulations, Parts 50 and 312 (21 CFR Parts 50 and 312). The deviations in Bosnia show that DOD has not corrected its procedures to prevent the recurrence of problems in the use of investigational products that arose during the Persian Gulf War.

The deviations described below do not give us confidence that DOD is at present capable of carrying out its obligations under INDs for drugs and biologics that are intended to provide potential protection to deployed military personnel. Inadequate recordkeeping has contributed to

> imperative that unit and theater commanders also cooperate with the study design to ensure compliance with the protocol. This is often not the case, as illustrated in the recent TBE vaccine study in U.S. troops in Bosnia. Many of the administrative errors in record keeping cited in the TBE study were due, in part, to the difficulty in directing the study from outside the theater of operations. The Human Use Review and Regulatory Affairs Division (HURRAD) is developing a policy that will require a protocol not start until the PI is in the theater of operations. This will ensure that the PI has control of the study and the authority to enforce the regulations and requirements that an IND study in human [sic] entails.

b. The USAMRIID clinical investigator responsible for study A7079 (LTC Pittman) stated that he was unable to go to Bosnia to conduct the study because of a ceiling on the number of people allowed into Bosnia, but he was later allowed one visit to Bosnia during which he conducted monitoring activities. On June 14, 1996, LTC Pittman wrote a memorandum to the Task Force Eagle TBE Vaccination Program Team Leader (LTC Kuschner) who had been delegated on-site responsibility for the study. The memorandum listed twelve types of documentation that should be maintained and forwarded to USAMRIID, including the following: vaccine inventory records, adverse reaction reports, credentials of study personnel, a plan for visiting the sites where subjects were vaccinated, "real time" documentation of protocol deviations, and clarification of subjects who had signed consent forms but for whom there were no vaccination records and for subjects who had been vaccinated but for whom there were no consent forms (memorandum enclosed). LTC Pittman did not receive a reply to this memorandum. Additionally, on July 29, 1996, LTC Pittman identified the deficiencies in the conduct of the Bosnian study in a memorandum to the Commander, USAMRMC (copy enclosed). A monitoring visit to Bosnia was planned for the fall of 1996, to be conducted by USAMMDA, the usual monitoring group. The monitoring trip was canceled due to redeployment of the American troops and the decision not to enroll subjects after September 1, 1996.

c. During FDA's inspection of TBE vaccine study protocol A5886, a comparison of an accelerated versus standard TBE vaccination schedule, Ms. Olin asked LTC Pittman, clinical investigator for the study, whether this study had ever been monitored. LTC Pittman responded that the study had never been monitored. USAMRIID had not received complete case history records or drug accountability records since implementation of the protocol.

3. Failure to ensure that the investigation was conducted in accordance with the protocol contained in the IND. [21 CFR 312.50]

In addition to the shortcomings in the conduct of the study mentioned above, there are additional failures in the conduct of the study.

a. The FDA inspection revealed that TBE vaccine was administered to four subjects who were non-U.S. citizens, a violation of the study's inclusion/exclusion criteria.

b. Many subjects were not administered the vaccine in accordance with the schedule specified in the protocol. Although we recognize that it is often difficult to obtain scheduling compliance by study subjects, significant deviations from the recommended regimen could confound the evaluation of vaccine safety and efficacy.

Please explain how the presence of the investigator in the theater of operations will necessarily ensure that the investigator will have control and authority to enforce the IND requirements, how the command structure will be changed so that the PI has the requisite control and authority over the conduct of the IND, and what other steps you intend to take to conduct studies in accordance with FDA-approved protocols and to adequately monitor the progress of all clinical investigations.

4. Promotion of an investigational new vaccine. [21 CFR 312.7(a)] Failure to obtain Institutional Review Board (IRB) approval of informed consent documents. [21 CFR 312.53(c)(1)(vi)(d)]

In a memorandum dated June 7, 1997, that included a response to the GAO's final report (copy enclosed), LTC Kuschner stated that he developed briefing documents that were used during the the Bosnian study. The document entitled "TBE Vaccine Brief" was to be read by trained medical personnel at the time of enrollment, and contains statements that promote that the TBE vaccine ". . . is already known to be *very safe* and *extremely effective* in preventing TBE" (emphasis in the original document). The document entitled "Task Force Eagle Mandatory Briefing on Tick-Borne Encephalitis" was to be read to all Operation Joint Endeavor military personnel, and contains the following statement: ". . . soldiers at high risk will be given the chance to receive a vaccine which is very safe and very effective in preventing infection with TBE."

Medical personnel involved with the informed consent process should present the known safety profile of the investigational agent and provide a balanced presentation of the possible benefits and risks associated with study participation. The language in the briefing documents is inconsistent with the language in the approved consent form because it does not outline the possible risks.

5. Clarification is requested as to whether DOD fulfilled its record keeping requirements.

According to the May 13, 1997, GAO report on the adequacy of DOD medical surveillance for deployments since the Gulf War, Army regulations require documentation in service members' permanent medical records of all immunizations received during military deployments. The GAO's review of medical records for 588 known recipients of the TBE vaccine found that there

was no documentation that immunization had been included in the permanent files of 141 recipients. Thus, 24 percent of these permanent records were inadequate.

This inadequacy persists despite DOD's recognition that it had similar problems during the Gulf War. In the attachment to Dr. Joseph's September 13, 1996, letter to Dr. Kessler (copy enclosed), commenting on the May 7, 1996, citizen petition submitted to FDA by Public Citizen Litigation Group, the National Veterans Legal Services Program, and the National Gulf War Resource Center, Inc., DOD stated:

> 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.

We understand that this TBE IND remains active. Please inform us as soon as possible as to how these deficiencies have been corrected.

B. Persian Gulf

The deviations identified in DOD's use of investigational products during the Persian Gulf War were similar to those identified in Bosnia and include, but are not limited to, the following:

1. Failure to meet the conditions set by the Commissioner for granting a waiver from the informed consent requirements under the Interim Rule for pyridostigmine bromide. [21 CFR 50.23(d)(2) and 312.56]

The interim rule states that the Commissioner, in reaching a determination that obtaining informed consent is not feasible, will ". . . take into account all pertinent factors, including, but not limited to: . . . (iv) The nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug." See 21 CFR 50.23(d)(2). In the Commissioner's January 8, 1991, letter to DOD, determining that obtaining informed consent was not feasible for pyridostigmine bromide, the Commissioner stated that

> Based on your agreement to provide and disseminate additional information to all military personnel concerning the risks and benefits of pyridostigmine, as stated in LTC Berezuk's January 8, 1991, letter to Dr. Stuart Nightingale, 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.

(Copies of both letters dated January 8, 1991, are enclosed.) FDA's agreement to waive the informed consent requirement was thus based, in large part, on DOD's agreement to provide and disseminate information on pyridostigmine to all military personnel.

In the attachment to Dr. Joseph's September 13, 1996, letter to Dr. Kessler, DOD stated that:

> There were also implementation difficulties in connection with the uniform provision of information to personnel regarding pyridostigmine.... 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.

In a survey conducted by DOD to determine the adequacy of the information provided to military personnel on the use of pyridostigmine, 47 percent of the respondents indicated that they received inadequate information. Based on DOD's statements, we conclude that the information sheet on pyridostigmine was not provided and disseminated to all military personnel in the Gulf as had clearly been anticipated as one of the conditions of the Commissioner granting the waiver under the interim rule.

2. Failure to collect, review, and make reports of adverse experiences attributed to the use of pyridostigmine in as timely a manner as conditions permit. [21 CFR 312.32 waived only the 3- and 10-day time limits for the reporting of serious and unexpected adverse events.]

Although the agency waived the requirements of 21 CFR 312.32 in regard to the 3- and 10-day time limits for the reporting of adverse experiences, we expected DOD to make a reasonable effort to collect, review, and make reports of "adverse clinical consequences attributed to the use of the treatment in as timely a manner as conditions permit." (See the December 11, 1990, letter to Dr. Clawson from Dr. Leber, enclosed) Although DOD conducted three retrospective surveys, these surveys represented a very small sampling of people who could have been aware of adverse events in people using pyridostigmine bromide, and they did not represent the level of effort that we expected from DOD. In response to agency requests for clarification of the Army's methodology for these surveys, the Army's October 27, 1994, IND amendment (copy enclosed) provided the following information:

> Following Operation Desert Storm, USAMRDC mailed questionnaires to the Commanding Officers of all Army medical hospitals deployed to the Gulf - active duty, National Guard and Reserve. Units deployed consisted of nine Mobile Army Surgical Hospitals, eight Combat Support Hospitals, twenty Evaluation Hospitals, three Field Hospitals, one General Hospital and one Station Hospital. These 42 units provided the medical care for the Army at Corps level and higher, including the XVIII Airborne corps.

Responses were received from 23 units (55%) and those responses were tabulated and provided as amendment 029. Doctor Temple noted that this survey indicated a much smaller population than the Keeler survey. One of the questions in the retrospective survey asked for the responders to report the number of personnel they were medically responsible for. The intent of the question was to identify a total population; however, the majority of the responders interpreted the question as asking for the number of medical personnel they were responsible for.

Colonel Keeler's survey in the XVIII Airborne Corps was conducted with medical officers at the Division and the unit level whereas the USAMRDC survey was conducted at the hospital level, in all areas of operation, including the XVIII Airborne corps.

Amendment 029 also provided the results of two additional smaller surveys. One was conducted in Army aviators and the other in Marine Corps aviators. Both of these surveys were also done at the unit level, similar to the Keeler study; however, here, the questionnaires were provided directly to the aviators and not to the medical personnel.

Given the apparent misunderstanding by responders to the scope of the survey (limiting responses to medical personnel rather than all personnel for whom they were medically responsible) and the response rate of only 55 percent, the first survey, which was expected to collect the most information, was of limited usefulness. In addition, the methodology does not mention any attempt to gather information from other branches of the military service present in the Gulf. Although DOD was expected to adequately collect serious and unexpected adverse events associated with the use of pyridostigmine bromide, this was not done.

3. Clarification is needed to determine if pyridostigmine bromide was labeled with language granted in waiver to 21 CFR 312.6. [21 CFR 312.6]

FDA agreed, as requested by DOD, to waive the provisions of 21 CFR 312.6 in order to allow DOD to employ the phrase "For military use and evaluation" in place of the statement ordinarily mandated for use on the immediate package of an investigational drug product, which reads "Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use." FDA's waiver of the standard statement (see enclosed letter dated December 11, 1990) was on condition that all product distributed to service members would carry the new "military use" labeling. However, in a September 28, 1994, letter (from Dr. Clawson to Dr. Leber, enclosed) FDA learned that there was no investigational labeling (i.e., neither the standard nor "military use" language) placed on the blister packs of pyridostigmine bromide that were stockpiled between 1985 and 1990. It is not clear from the information provided whether the pyridostigmine bromide that was distributed to military personnel in the Persian Gulf was labeled as required by the conditions of the waiver.

4. Failure to ensure that the investigation is conducted in accordance with the general investigational plan for the botulinum toxoid vaccine. [21 CFR 312.50]

The protocol for the botulinum toxoid vaccine (copy enclosed) stated that each botulinum toxoid vaccine dose was to be recorded in the individual's permanent immunization record. On May 19, 1997, Dr. Johnson from FDA's Center for Biologics Evaluation and Research (CBER) called Dr. Rick Kenyon and Dr. Doug Reichard and asked whether this had been done; later that day, Dr. Kenyon faxed to CBER the Army's response (copy enclosed):

> Which units received the vaccine was, and remains, classified. For this reason, no notation was made in the permanent record. However, unit records may have been kept. We have been unsuccessful in retrieving any substantial information.

5. Failure to maintain adequate records showing the receipt, shipment, and disposition of the investigational product botulinum toxoid vaccine. [21 CFR 312.57 and 59]

DOD recorded the number of doses of the botulinum toxoid vaccine shipped and returned following the Gulf War and has stated that the vaccine was given to approximately 8,000 individuals. However, the documentation for the number of doses returned plus the number of doses administered to the reported 8,000 service members does not total the number of doses shipped. DOD stated that records of vaccine destruction were not maintained because its use occurred in a war zone.

6. Clarification is requested as to whether DOD met the conditions for the Commissioner granting a waiver from the informed consent requirements under the Interim Rule for botulinum toxoid vaccine [21 CFR 50.23(d)(2)] or whether informed consent was obtained in accordance with 21 CFR 50.27. In addition, it is not clear whether records were retained as required by 21 CFR 312.57.

It is not clear from DOD's actions whether the criteria for granting the original waiver under the interim rule were met, specifically that ". . . preservation of the health of the individual and the safety of other personnel require that a particular treatment [the botulinum toxoid vaccine] be provided to a specified group of military personnel, without regard to what might be an individual's personal preference for no treatment or for some alternative treatment."
If the criteria were not met, then DOD was required to obtain and document the informed consent of military personnel receiving the vaccine in accordance with 21 CFR 50.25 and 50.27.

According to Dr. Mendez's March 15, 1991, letter to Dr. Kessler (copy enclosed), a decision was made to administer the vaccine on a voluntary basis to military personnel. In an attachment to Dr. Joseph's September 13, 1996, letter to Dr. Kessler, the following explanation is given for this decision:

> When the vaccine, which was in very limited supply, and the 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.
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> . . . 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.'

In Senator Rockefeller's May 16, 1994, letter to you, submitting questions in follow-up to the May 6, 1994, oversight hearing, Senator Rockefeller's requested ". . . copies of all informed consent forms signed by military personnel in the Persian Gulf who received an investigational drug." Your response stated, in part:

> 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. Although there was no informed consent required, there was a decision made by the command structure in the theater of operations to use informed consent for the botulinum vaccine. Attached is the information about the botulinum vaccine presented to individuals and a sample of the informed consent form used. Unfortunately, to date, we have not been able to obtain the original informed consent forms used in the theater of operations, however, our efforts will continue until all avenues have been exhausted.

(Copies of the May 16, 1994, letter and the response are enclosed.) Without signed consent forms to document that informed consent was obtained, and based on testimony from Persian Gulf War veterans that information on the vaccine was not uniformly given to military personnel (presented at the Rockefeller hearing and at the January 12, 1996, public meeting of the

Presidential Advisory Committee on Gulf War Veterans' Illnesses), we are unable to verify that informed consent was obtained from military personnel who received the botulinum toxoid vaccine.

We, therefore, need to know whether informed consent was obtained from all military personnel who received the botulinum toxoid vaccine and what documentation exists to verify that informed consent was obtained. If informed consent was obtained, please provide a copy of the sample consent form used for this protocol and provide documentation that the consent form was reviewed and approved by your IRB. If signed consent forms have not been found, please describe the steps DOD will take in the future to ensure that such records are retained and retrievable.

All individuals receiving the botulinum toxoid vaccine were to have access to information in a vaccine information sheet which provided pertinent details of the immunization and procedures, and these individuals were to be allowed to ask questions regarding the vaccine prior to its administration. DOD finalized an information sheet for this vaccine on January 2, 1991. There is no information available about the number of individuals who received the information in the information sheet prior to immunization or whether these individuals were allowed to ask questions (and receive answers) prior to immunization. Given DOD's statements that efforts to distribute information on pyridostigmine were frustrated by the limited time available (see item 1 above), we request clarification as to whether individuals were provided the information in the vaccine information sheet and, if so, how.

C. Summary

These regulatory deviations, taken as a whole, point to an underlying inability for DOD to carry out its obligations under INDs for drugs and biologics intended to provide potential protection to deployed military personnel. We would welcome your views as to the underlying problem(s) and potential solutions to the problem(s). We suggest that DOD's difficulties may result, in part, from a discontinuity between the military command that plans the IND study and provides assurances to this agency and the command that ultimately must carry out the study. This discontinuity in command appears to occur within the Army itself (e.g., personnel from the Office of the Surgeon General, Department of the Army submit the IND, but the administration of the IND is carried out by other combat command structures in the Army) and may occur DOD-wide (the Department of the Army's INDs provide for the administration of investigational products to personnel in other military services). We believe that unless the command(s) that provides assurances to this agency about the conduct of the IND have control of, or at least substantial influence over the actual conduct of the IND, there will be continued difficulties of the types cited above.

The IND for pyridostigmine bromide (IND 23,509) illustrates the discontinuity well. The IND is held by the Department of the Army. The language in the IND for the use of pyridostigmine in

the Persian Gulf at times refers to the Army and other times refers to the DOD. The IND submission did not make clear, however, whether the Army had the authority to represent DOD and all of its branches. In a November 3, 1994, letter to the Army (copy enclosed), the agency raised this issue and noted ". . . that the Department of the Army is the sponsor of this IND, yet we are aware that other branches of the Armed Forces have used this drug, and will use it in the future, should it become necessary. For this reason, we ask that you assure that these other branches are administratively included under the IND." The agency has not received a response to this request nor a description of how adequate control over the administration of an IND can be accomplished DOD-wide. As indicated above, we believe the lack of control and accountability may have been a cause of the deficiencies described above.

We have previously discussed most of these concerns with various DOD personnel over the last several years. We are concerned that a number of the lessons that should have been learned from the Gulf War have not led to corrections that should have been demonstrated in Bosnia. Because of the recurrence of deviations from FDA regulations noted above, we ask that you inform us, in writing, by October 21, 1997, of the steps you have taken or plan to take to comply with the regulations. We need to know this not only because of ongoing trials, but also as part of our reconsideration of the interim rule that permitted a waiver of the informed consent requirement.

In addition to the questions raised above, we request that, at a minimum, you specifically address the following questions in the information you provide:

1. DOD acknowledged in its response to the GAO report that the unit and theater commanders did not always cooperate with the study design to ensure compliance with the TBE vaccine protocol. This was substantiated by our inspection of the TBE vaccine study. How will DOD ensure that IND commitments are fulfilled in combat or deployment situations? Who in DOD will provide the necessary assurances to FDA that IND commitments will be met? Which parts of DOD would have to make commitments to follow the IND regulations in order for a study to be conducted in compliance with FDA regulations?

2. How will DOD ensure that adequate records showing the receipt, shipment, and disposition of investigational products are maintained?

3. How will DOD ensure that documentation of immunizations (or use of other investigational products) are included in all service members' permanent medical records?

4. How will DOD ensure that the collection, review, and reporting of adverse clinical consequences attributed to the use of an investigational product are timely and complete?

5. For self-administered products such as pyridostigmine bromide, what are DOD's detailed plans for recording which soldiers are ordered to (and actually do) administer the

product, and for obtaining information about adverse events in all soldiers exposed to the product?

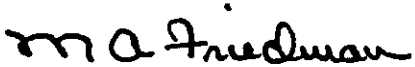
6. How will DOD ensure that military personnel are provided information sheets on investigational products?

7. How will DOD ensure that investigational products supplied to service members are labeled as required by 21 CFR 312.6?

8. How will DOD ensure that the ongoing use of investigational products immediately conform to FDA's IND requirements?

Should you need assistance or have any questions or comments about the contents of this letter or any aspects of clinical testing of drugs and biologics, please contact Dr. Robert Temple concerning drugs at (301) 594-6758 and Dr. Karen L. Goldenthal concerning vaccines at (301) 827-3070.

Sincerely yours,



Michael A. Friedman, M.D.
Lead Deputy Commissioner

Enclosures

cc:
Ronald E. Clawson, Ph.D.
SGRD-HR (Human Use Review & Regulatory Affairs)
Office of the Surgeon General
Department of the Army
U.S. Army Medical Research and Development Command
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Enclosures

Tab 1 - April 11, 1997 response to GAO report

Tab 2 - June 14, 1996 memorandum from Dr. Pittman

Tab 3 - July 29, 1996 memorandum from Dr. Pittman

Tab 4 - June 5, 1997 memorandum from LTC Kuschner

Tab 5 - September 13, 1996 letter from Dr. Joseph

Tab 6 - January 8, 1991 letter from Dr. Kessler

Tab 7 - January 8, 1991 letter from LTC Berezuk

Tab 8 - December 11, 1990 letter from Dr. Leber

Tab 9 - October 27, 1994 letter from Major Vander Hamm

Tab 10 - September 28, 1994 letter from Dr. Clawson

Tab 11 - October 15, 1990 protocol for Pentavalent Botulinum Toxoid

Tab 12 - May 19, 1997 fax from Dr. Kenyon

Tab 13 - March 15, 1991 letter from Dr. Mendez

Tab 14 - May 16, 1994 letter from Senator Rockefeller and DOD response

Tab 15 - November 3, 1994 letter from Dr. Katz for Dr. Leber