APPENDIX AA

AUGUST 30, 1990

MEMORANDUM OF MEETING BETWEEN THE DEPARTMENT OF DEFENSE AND THE FOOD AND DRUG ADMINISTRATION

SGRD-UMP 30 August 1990

MEMORANDUM FOR RECORD

SUBJECT: Proceedings of Meeting Between FDA and DOD Regarding Operation Desert Shield

1. The purpose of the meeting was to review issues pertaining to the regulatory approach to deploy necessary medical products currently in IND status in Support of Operation Desert Shield. The meeting began at 1315 hours. Those in attendance from the FDA included Associate Commissioner Nightingale, Chief Counsel Porter, Center for Drugs Director Dr. Peck, Deputy Director for Drug Review I Dr. Botstein, Ms. Witt (General Counsel), Ms. Lorraine (General Counsel), Center for Biologics Deputy Director Dr. Elaine Esber, Deputy Dir Assoc Commissioner Mr. Duncan, Director Drug Evaluation II Dr. Bilstad, Ms. Wion (General Counsel), Mr. Hoeting - Office of Compliance, Mr. Geyer (General Counsel), and several other distinguished FDA personnel. Those from the Department of Defense were Lt Col Lehmann, LTC Berezuk, Dr. Clawson, Dr. Brandt, and Mr. Winchester.

2. Discussion was oriented to the unusual circumstances and military medical needs of Defense in support of Operation Desert Shield. Attention was focused primarily on the issue of informed consent. Other topics of discussion included investigational labeling, other sections of the IND regulations, and the FDA-DOD Memorandum of Understanding.

a. FDA expressed some concern about liability and the need to comply with the regulations. Mr. Winchester reviewed the Feres Doctrine and cited a case of applicability of the Doctrine to a Federal Agency other than Defense.

b. Investigational framework. Dr. Peck pointed out the need to establish an appropriate investigational framework to collect observational data and evaluate the military medical products in question. It was recognized that data collection could not occur during military conflict. However, medical personnel can be apprised of what to look for to facilitate retrospective analyses. He suggested that labeling the diazepam autoinjector, "For military Use and Evaluation Only" might facilitate this process. Similar labeling could be applied to all soldier carried medical items with investigational status.

c. It was pointed out that use of the export regulation obviates the applicability of the IND regulations.

d. Ms. Porter pointed out that the investigational status of the nonapproved products cannot be abandoned altogether.

3. The attached worksheet was used as a guide to address CFRs of concern to Defense. The following are those concerns and a brief synopsis of the discussion:

a. 21 CFR 312.6 - Labeling of an Investigational New Drug. Defense cannot comply with the requirement to label service member carried investigational medical products, "Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use". Labeling such as "FOR MILITARY USE ONLY" is acceptable for service member carried items. Like informed consent, "investigational" labeling itself could undermine the soldier's confidence in the treatment or possibly result in nonuse of the treatment altogether. In addition, such labeling may undermine and damage the soldier's confidence in the chain of command, and adversely impact on morale and discipline. Immediate relief from the requirement for investigational labeling by waiver or by issuance of a new regulation is requested.

DISCUSSION. This is a problem only for soldier carried items. Labeling as, "FOR MILITARY USE AND EVALUATION ONLY" appeared to be an acceptable compromise. Investigational products handled only by health care providers could still be labeled as required in the CFR. The FDA Chief Counsel believes that the labeling requirement can be waived under the existing regulations, however, further internal consultation is required.

b. 21 CFR 312.7 - Promotion and Charging for Investigational Drugs. Defense needs to be able to buy investigational medical products from manufacturers to meet Defense needs. Such purchases cannot be considered "commercialization". Would the fact that a manufacturer and holder of an IND sells the investigational product to Defense for a profit violate this regulation? Clarification is requested.

DISCUSSION. Commercialization would occur only if the medical product were to be sold to the soldier, an event that will not occur.

c. 21 CFR 312.32 - IND Safety Reports. In armed conflict and in circumstances of potential armed conflict, for deployed or deployable units, Defense cannot comply with the requirement to submit safety reports of adverse experience no later than three working days after receipt of the information, nor can Defense comply with the requirement to submit a written report of the adverse experience within ten working days. Defense can submit safety reports as soon as military circumstances permit and the information becomes available. Modification of this FDA requirement for submission of safety reports by waiver or by issuance of a new regulation is requested.

DISCUSSION: It is agreed that the reporting time requirements

cannot be met. Filing of safety reports as expeditiously as the military situation permits is acceptable. Under the existing regulations, the appropriate Center Director and the Sponsor can agree on the time of reporting. A waiver is not required, and an amendment to the regulation is not required.

d. 21 CFR 312.33 - Annual Reports. Defense can submit annual reports.

e. 21 CFR 312.40 - General Requirements for Use of an Investigational New Drug in a Clinical Investigation. The reference to 21 CFR 50, the requirement for informed consent, cannot be complied with in armed conflict and in circumstances of potential armed conflict for deployed and deployable units. Immediate relief from the requirement of informed consent by waiver or by issuance of a new regulation is requested. Defense can comply with the requirements for IRBs referenced in 21 CFR 56.

DISCUSSION: The informed consent issue is addressed below.

f. 21 CFR 312.50 - General Responsibilities of Sponsors. Sponsors for investigational medical products needed by Defense may be the military department surgeons general or other sponsors such as commercial pharmaceutical, biologics, or medical device manufacturers. The wording in the new regulation needs to take this into consideration.

DISCUSSION: Commercial sponsors have no reason to deny Defense permission to cross reference INDs thereby allowing Defense to sponsor the IND.

g. 21 CFR 312.53 - Selecting Investigators and Monitors. In armed conflict and in circumstances of potential armed conflict for deployed and deployable units, Defense cannot comply with these requirements. The concept of an investigator, and investigator responsibilities in these circumstances is incompatible with the operational realities of applied military medicine. The control of the investigational inventory and supplies as stated in existing FDA regulations cannot be fully accomplished. Access to the investigational products will be controlled by Defense personnel. The distribution and use of investigational products will be controlled and monitored in the same manner as other medical supplies. Relief from or modification of these regulatory requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA indicated that Defense should do "the best we can" to control inventory in a combat environment. A waiver or revision of the regulation is not required.

h. 21 CFR 312.55 - Informing investigators. In armed

conflict or in circumstances of potential armed conflict for deployed and deployable units, Defense may not be able to comply with requirements for an investigator brochure. There may not be an investigator, or there may not be an investigator at the time the investigational medical products are used. Information on safety and use of investigational medical products will be provided to medical and paramedical personnel, and to individual service members for investigational products intended for self administration. New information regarding safety and efficacy will be provided to the appropriate personnel. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA agreed that this requirement is met if pertinent information is provided in any form (technical reports, field manuals, updated information, etc) to military medical personnel such as field physicians. Waiver or revision of the regulation is not required.

i. 21 CFR 312.57 - Recordkeeping and Record Retention. In armed conflict or in circumstances of potential armed conflict for deployed and deployable units, Defense cannot comply with requirements to record the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment. The total quantity of investigational product used in these circumstances will be recorded in accordance with normal military medical inventory procedures. The retention of such records will be in accordance with standard military regulations. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA requested and Defense agreed to provide a copy of military regulations governing handling and control of distribution of scheduled substances like morphine, and the procedure for controlling atropine autoinjectors, in a field environment. This issue remains open.

j. 21 CFR 312.59 - Disposition of Unused Supply of Investigational Drug. Given the chaotic nature of armed conflict, Defense cannot assure the return of all unused supplies of an investigational medical product distributed in support of service members in armed conflict or potential armed conflict. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION. See above discussion under paragraph i. This issue remains open.

k. 21 CFR 312.60 - General Responsibilities of Investigators. In instances where investigational medical products are distributed in support of service members in armed

conflict or in potential armed conflict, Defense cannot comply with requirements that the investigator will conduct the investigation according to the signed investigator statement, or the investigational plan; or the obtaining of informed consent from each subject to whom the investigational medical product is administered. This is because the concept of an investigator may not feasible in armed conflict or in circumstances of potential armed conflict for deployed and deployable units. The prohibitive nature of informed consent under these circumstances has been discussed. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION. An investigational plan that is acceptable to Defense should be submitted with the IND (ie, for a retrospective survey).. Informed consent is a separate issue discussed below. Dr. Peck stated his concern that some form of an investigator should be contemplated for retrospective data collection. For example, an investigator who is remote from the battle theatre can be appointed who is responsible for obtaining, organizing and evaluating retrospectively collected data. It was recognized that investigator activities traditionally associated with an investigational medical product study are not possible under conditions of military conflict.

l. 21 CFR 312.61 - Control of the Investigational Drug. In circumstances of armed conflict or in potential armed conflict, Defense cannot comply since investigators and subinvestigators may not directly supervise the administration of the investigational medical product. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA Chief Counsel stated that drug administration responsibilities of investigators and subinvestigators need to be addressed by FDA further. This issue is open.

m. 21 CFR 312.62 - Investigator Recordkeeping and Record Retention. In armed conflict and in circumstances of potential armed conflict for deployed or deployable units, Defense cannot comply with requirements for recording disposition of the drug, case histories, and requirements for record retention since placement of an on-scene investigator may not be possible in these circumstances. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: The FDA and Defense agreed that some level of recordkeeping, case histories, etc, can be accomplished in a hospital setting (by way of medical charts for example), but not in a field setting. Waiver or revision of the regulation is not required.

n. 21 CFR 312.64 - Investigator Reports. Though the concept

of an investigator may not be feasible in armed conflict and in circumstances of potential armed conflict for deployed and deployable units, Defense will attempt to collect and provide information on safety and efficacy for investigational medical products used in these circumstances. Retrospective information collection is likely to be most feasible. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: Investigator reports will depend on the type of investigator and investigation as described above. Waiver or revision of the regulation is not required.

o. 21 CFR 312.66 - Assurance of IRB Review. Defense will obtain IRB review and approval and will report to the IRB all changes in the information collection activity and unanticipated problems involving the use of the investigational medical product.

p. 21 CFR 312.68 - Inspection of Investigators Records and Reports. Regardless of whether or not an investigator is involved, FDA will have access to Sponsor and DOD records and reports associated with the use of investigational medical products. FDA access to classified documents will require the appropriate security clearance.

312.69 - Handling of Controlled Substances. Investigational controlled substances deployed with a deployed unit, in armed conflict and in circumstances of potential armed conflict, will be handled in accordance with existing Defense regulations for securing substances subject to the Controlled Substances Act. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: See paragraph i above.

4. IND products for deployment by Defense will be considered on a case-by-case basis by FDA.

5. FDA raised the question of who resolves the impasse if FDA decides that it is inappropriate to deploy a particular investigational product that Defense wants to deploy? This question is not addressed in the FDA-DOD Memorandum of Understanding, and it was not resolved during this meeting.

6. Options summarized by Chief Counsel Margaret Porter, FDA, for resolving the informed consent issue.

a. For products in investigational status exported from US and used overseas, and not used in the US:

(1) The export licensing requirement cited in 21 CFR

312.110 is the quickest and most feasible approach. The IND regulations are not applicable under this export licensing provision - ie informed consent and investigational labeling are not required.

(2) In addition, the FDA will conduct a safety review for each product under consideration.

(3) In addition, as provided by the FDA-DOD MOU, the FDA will review available data to determine if use in an expanded military population is appropriate.

b. For investigational medical products used in the US, such as vaccines, amendment of the informed consent regulations, 21 CFR Part 50, signed by Secretary HHS, will be necessary. Coordination through OMB may be required. This overall process will take weeks. Since time does not permit publication of a notice of proposed rulemaking for public comment, a public announcement before finalizing the amendment will be necessary. Drafting of an amendment to the regulation is underway at FDA.

7. Since administration of appropriate medical products under IND is expected to be necessary both inside the US and overseas, both options outlined by Chief Counsel Porter appear to be necessary.

8. Diazepam Autoinjector regulatory approach. Deploying the diazepam autoinjector in support of Operation Desert Shield is a primary objective. The diazepam autoinjector will be produced overseas and is expected to be delivered overseas in about four weeks in support of Operation Desert Shield. In this circumstance the export licensing regulation is not applicable. An FDA safety review, and an FDA determination if use in an expanded military population is appropriate will suffice for deploying the diazepam autoinjector in support of Operation Desert Shield. Informed consent will not be required.

9. FDA and DOD recognize the urgency of the situation. Considerabe progress was made during the meeting. Further discussions, interactions, and meetings will continue. Ms. Lorraine and Lt Col Lehmann will continue to be the points of contact for the FDA and Defense, respectively.

Encl

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