ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS
Request 112994-A

Q.1. Which Agency or component within DoD fund extramural research? (Your August 25 response to Q.6. says that the clinical investigation programs within the military services does not currently support extramural research.)

A.1 Essentially all major component commands and Agencies, except for clinical investigations programs, possesses the authority to fund extramural research. However, the extent to which such extramural research involves participation of human subjects can vary from no participation to multiple project participation.

Q.2. Please characterize the population of human subjects involved in DoD intramural research today. Are these subjects active duty military personnel, civilian DoD employees, or non-employees? Veterans?

A.2. Intramural research which involves a human subject is principally directed to active duty military personnel. However, it is possible that a research protocol would permit participation by civilian DoD employees or contract personnel working on a project, i.e. blood analyses for marker enzymes, antibodies, viral load, etc. Clinical investigations programs are limited by the beneficiary population which the military medical system services. This includes Active duty personnel and their dependents, retired military personnel and dependents, and individuals authorized military health care access by Act of Congress.

A.3. Do the experimental studies performed by medical treatment facilities involve patients only or healthy volunteers as well?

Q.3. Dependent upon the nature of research and the protocol design, it is possible that a matched cohort population of normal healthy individuals may be required for comparison purposes against the subject or test population in question.

A.4. Do the military medical research labs and institutes conduct studies involving patients or healthy volunteers only?

Q.4. When the term "patient" is used it presumes clinical studies or research protocols that are conducted in conjunction with a medical facility. Dependent upon the type of study, i.e. AIDS/HIV, infectious diseases related to deployment, etc may be conducted at a medical facility with participation by

investigators associated with military research facilities. Dependent upon the nature of research and the protocol design, it is possible that a matched cohort population of normal healthy individuals may be required for comparison purposes against the subject or test population in question.

Q.5. Please characterize the human subject population involved in extramural DoD-sponsored research. Does such research ever involve DoD employees, military or civilian, as research subjects? Veterans? Patients or healthy volunteers, or both?

A.5. The human subject population involved in extramural DoD-sponsored research is dependent upon the research study design. Extramural funding for programs such as womens' health, breast cancer, vaccine development may include military, their dependents, and/or civilians based upon the population requirements of the protocol. Dependent upon the nature of research and the protocol design, it is possible that a matched cohort population of normal healthy individuals may be required for comparison purposes against the subject or test population in question.

Q.6. Are foreign nationals ever involved as research subjects in DoD-sponsored research? in the U.S. or at facilities abroad?

A.6. DoD sponsors and collaborates in research activities with various foreign universities, Ministries of Health, U.S. sponsored agencies, and foreign military medical agencies. Such programs of cooperative research are frequently conducted in the host country. In circumstances where host nation human subject participation is involved, the guidelines for human subjects participation must be as stringent as those of the U.S. Where differences between U.S. and a host nation's standards differ, the more restrictive standard will apply.

Q.7. In your August 25 answer to Q.1. you state that medical monitors are assigned to each study involving more than minimal risk. How do these monitors oversee ongoing research? To whom do they report their findings, the principal investigator or the IRB or to someone else?

A.7 Medical monitors are required to be familiar with the protocol and to discuss the project with the principal investigator in terms of patient management and safety. The medical monitor is independent of the investigation team and serves primarily as the patient advocate. The monitor discusses research progress with the principal investigators, interviews patient subjects, consults on individuals cases, and is primarily interested in the safety and well being of the research subject. Depending upon the nature of a finding, the medical monitor reports such information to the principal investigator

for corrective action, to the Chairman of the Department sponsoring the research, and to the Chairman of the IRB. Under law, Title 21 Code of Federal Regulations, adverse events associated with an investigational new drug or device (IND) must be reported to the Food and Drug Administration.

Q.8 What kinds of training costs are incurred by DoD's medical treatment facilities, research labs, and institutions in the course of conducting research with human subjects? Please elaborate upon your August 26 response to Questions 3 and 8 regarding increases in training costs due to the demands of human subject protection policies.

A.8 As indicated in A.3, there are no specific operating budget data maintained at the various levels specific to training expenses related to human subjects protection activities. These expenses are covered under the general category of operational expenses. As noted in A.8, the significant interest of various Congressional Committees, Subcommittees and Select Study Groups regarding the use of human subjects during the period covering 1939 to present has placed an unplanned demand for document searches and reporting requirements. Based upon the heightened level of awareness of past histories of human subjects participation, the various Federal Agencies have all increased the levels of awareness training to personnel involved in human subjects research.

Q.9. How are any adverse effects on research subjects (injury, disability, or death of persons involved in a research protocol) reported to and by the local IRB/institutional human use committee? Where are records of such adverse outcomes maintained and reviewed? With the IRB? The military service? Headquarters? How does the DoD respond to these incidents?

A.9 Adverse events would be reported to the Chairman of the IRB in a memorandum format along with other supporting documents depending upon the nature of the adverse event. Again, depending upon the nature of the event, additional reporting should be made to the Chairman of the Department sponsoring the research, the Commanding Officer of the facility, the military chain of command, and if required the Food and Drug Administration. These reports are reviewed by the IRB, and the Service's Human Subjects Protection Office for action. The reports are held as documents within the facility conducting the research and as correspondence within the military chain of command. The response by DoD is situational and is dependent upon the nature of events. The scope or response may range from a request of an incident report to a Article 32 Investigation under the Uniform Code of Military Justice.

Q.10 What kinds of audits or reviews or IRB performance are conducted by Service or agency headquarters? (follow-up to the August 25 response to Q.4.)

A.10 The Services conduct announced and unannounced site visits to facilities to evaluate program management and to audit compliance with regulations. Over the past 3 years, the Services have conducted approximately 180 such visits by local or headquarter authorities of facilities conducting human subjects research. This number does not include all of the internal quality assurance committee monitoring programs, or periodic administrative and record keeping audits that are conducted.

Q.11 What sanctions, if any, does DoD impose on non-compliant IRBs or investigators?

A.11 A broad range of sanctions can be imposed at the local Command, Headquarters, Service or DoD level. These include temporary or permanent cessation of fiscal support to a project, as well as removal of investigator privileges. For military personnel sanctions could include letters of reprimand, non-judicial punishment or other sanctions which fall under the jurisdiction military courts. For civilian personnel, sanctions range from letters of reprimand, suspension, or termination of employment as covered under the civilian personnel regulations.

Q.12 What kinds of documents relating to the planning, conduct, effects and results of DoD-sponsored or conducted research involving human subjects are publicly available, either by FOIA request or published announcements and reports, e.g., departmental planning documents, contract or grant solicitations, solicited or unsolicited research proposals, the records of institutional review committees, or interim and/or final research project reports?

A.12 The Freedom of Information Act and the Privacy Act defines the types of documents that are accessible to the public. Documents that would not be releasable would be classified documents, information which violates the privacy rights of individuals, working papers, draft documents, internal memorandums, or documents which compromise proprietary or intellectual rights to patent applications or cooperative commercial ventures.

Q.13 Does DoD now conduct or fund any classified research involving human subjects? In what ways do project review and oversight differ from those procedures used for unclassified research? What would make such research classified? For example, might

the purpose or application of the research be classified while the protocol itself is not? Or the findings classified but not the plans to undertake the research? Or are projects always classified in their entirety?

A.13 There is no current classified research involving human subjects funded by DoD. All research proposals involving human subjects, independent of classification status, must follow Title 32, Code of Federal Regulations, Part 219 and other applicable Federal Laws and Regulations. IRB review of classified proposals would demand the membership to possess the appropriate security clearances. The Food and Drug Administration does have personnel with clearances who can review classified investigational new drug or device (IND) proposals. Classification requirements are situational and am therefore reluctant to make a sweeping characterization of information release. Classification standards are covered primarily in two DoD Directives 5200.1, "DoD Information Security Program" and 5230.9, "Clearance of DoD Information for Public Release."

Q.14 Your August 25 response to Q.9 about potential waivers of the applicability of the Common Rule states that notification of OPRR and a Federal Register announcement are required, but that this exceptions process has never been invoked. What are the kinds of circumstances, hypothetically speaking, that might prompt DoD to seek such a waiver? What are the deliberative and decision procedures that would be followed within DoD if such an exception to the Common Rule were contemplated?

A.14 The mission of the Department in defense of the territories and interests of the Nation are global and situational. This can vary from a state of national emergency to a peace time tempo of operations. Laws are man made and therefore recognized as potentially limited in circumspection. Military situations may occur where the safety and well being of an individual or group may require a decision to be made to either violate a law or do nothing secure only in the knowledge of having upheld the law. To preclude being limited to such a choice, the ability to waiver parts of the law, with appropriate caveats, provides an alternative under the law.

With full consideration of the Belmont Report, the deliberations between DoD and the Food and Drug Administration formulated the decision to permit the use of pyridostigmine and botulinum vaccine as a therapeutic countermeasure to a perceived threat during the Persian Gulf War. This may be the most current example of the deliberative processes employed in a contingency situation. These two biologics were not deployed for research purposes but rather as the best available therapeutic countermeasures to known chemical or biological agents of warfare.

5 Are there any other procedures or circumstances under which the DoD could conduct or sponsor research with human subjects that does not follow the Common Rule or that takes place in secret?

A.15 Title 32, Part 219, Title 45 Part 46, subparts B,C, and D, Title 21 Volumes I and II and other regulations found in Federal statutory law form the basis of DoD conduct of human subjects research.

Q.16 During Operation Desert Shield, the DoD sought and received waivers through FDA regulations governing informed consent requirements for investigational drugs and biologicals, so that an investigational new drug and a vaccine could be administered to troops. (Federal Register vol 55, no. 426, Dec 21 1990.) What kinds of follow-up studies were conducted with the troops who received the vaccine or drug under this waiver to assess efficacy, reactions or side effects? Please provide any records and reports that pertain to decision to seek the waiver from FDA regulations or that assess the effects of either the drug or vaccine on the troops involved.

A.16 A retrospective study of health care providers was conducted based on the Operation Desert Storm experience. This study was published as Keeler, J.R., Hurst, C.G., and Dunn, M.A., Pyridostigmine Used as A Nerve Agent Pretreatment Under Wartime Conditions, Journal of the American Medical Association, volume 266, pages 693-695, 1991. A copy of this article is attached as enclosure 1.

Retrospective studies and clinical evaluations of experiences with pyridostigmine bromide during Operation Desert Shield/Storm have been reported by Sharabi, Y., et al., Survey of Symptoms Following Intake of Pyridostigmine During the Persian Gulf War, Israeli Journal of Medical Science, volume 27, pages 656-658, 1991, and Almog S., et al., Acute Pyridostigmine Overdose: A report of Nine Cases, Israeli Journal of Medical Science, volume 27, pages 659-663, 1991. These publications have been referenced in the pyridostimine bromide New Drug Application and copies of these articles are attached as enclosure 2.

The requested documentation to the Food and Drug Administration (FDA) dated 28 December 1990 seeking a waiver of informed consent for pyridostigmine bromide 30 mg. tablets under the provisions of Title 21, Code of Federal Regulations, Part 50.23 (d)(1) is attached as enclosure 3. A supporting letter from the Director, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, dated 4 January 1991, along with the Minutes of the Meeting of the Human Subjects Research Review Board, dated 10 October 1990, which reviewed the proposed use of pentavalent botulinum toxoid to at-risk individuals during Operation Desert Shield

is attached as enclosure 4 The FDA approval of this waiver, dated 8 January 1991, is attached as enclosure 5.