DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS

U.S. SENATE

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STATEMENT BY THE FOOD AND DRUG ADMINISTRATION
CONCERNING THE USE OF UNAPPROVED DRUGS
DURING OPERATION DESERT STORM

The following statement is provided for the hearing of the Committee on Veterans' Affairs, United States Senate, May 6, 1994, on the subject of the use of investigational drugs without obtaining informed consent during Operation Desert Storm/Shield.

As the Committee knows, following a request from the Department of Defense (DoD), the Food and Drug Administration (FDA) granted waivers from current informed consent regulations for the use of two products in specific protocols: pyridostigmine and botulinum toxoid vaccine.

Pyridostigmine

Pyridostigmine has been approved by FDA since 1955 for the treatment of myasthenia gravis, a chronic disorder characterized by muscle weakness. As a result, there is considerable human experience on its long-term use. Further, the DoD has been investigating the effects of pyridostigmine pre-treatment on healthy soldiers under an Investigational New Drug (IND) application on file with FDA since 1984. No serious adverse reactions were reported in this population from this experience.

The determination that pyridostigmine could be administered safely to healthy soldiers during Operation Desert Storm under

the IND was based primarily on the long experience with pyridostigmine at doses considerably greater than those proposed as pre-treatment for organophosphate nerve agent exposure, (30 mg three times a day for a maximum of 7 days). Patients with myasthenia typically are treated with pyridostigmine doses of up to 1500 mg a day for many years. While myasthenic patients are not, of course, entirely healthy, we believed their experience was pertinent to the effects of pyridostigmine in completely healthy individuals. Patients with myasthenia gravis have antibodies directed at skeletal muscle structures. They would be expected to differ from healthy persons with respect to effects of pyridostigmine on skeletal muscle, and be less likely to develop muscle twitching and muscle cramps. But in other respects, their response should be similar. We knew from past experience with the use of this drug that side effects (e.g., abdominal cramps, nausea, diarrhea, rash, muscle weakness, dimmed vision) were possible, and these were described in the DoD's Field Manual, which was included in the IND submission.

In addition, broad acceptance of the safety of the proposed dosing regimen can be found in the medical literature (an article in the Medical Letter of November 16, 1990, and an article by Dunn and Sidel in the Journal of the American Medical Association on August 4, 1989). (Copies of these are provided for the record).

The effectiveness of pyridostigmine, given as pre-treatment in conjunction with the acute use of atropine and 2-PAM (the regimen being used in this instance), in decreasing toxicity of nerve agents in humans, has not been demonstrated. In monkeys however, the regimen greatly increases the lethal dose of nerve agent compared to the lethal doses in untreated monkeys. Despite the lack of human data on protection (it would be unethical to administer toxic agents to subjects for such research), pyridostigmine, in conjunction with the acute use of atropine and 2-PAM appears to be the best available means of decreasing organophosphate nerve agent intoxication. It has been available to NATO armies and has been held in reserve by DoD for that use since 1986.

The Agency has reviewed Chemistry and Manufacturing Controls data for pyridostigmine bromide on a continuing basis. Additionally, under a long-standing agreement with the DoD, Agency chemists periodically reviewed stability study data from studies conducted on pyridostigmine bromide tablets stockpiled by DoD at various locations to be available in time of war for distribution and use by military personnel. The Agency has concluded that the two primary suppliers of the drug provide acceptable products.

Botulinum Toxoid Vaccine

With regard to the botulinum toxoid vaccine, there is no satisfactory alterative product to prevent botulism. This vaccine has been provided for over 20 years to laboratory workers and public health professionals at risk of infection. This has been accomplished under an IND sponsored by the Centers for Disease Control and Prevention (CDC). FDA has reviewed data and information on this use in annual reports to the IND submitted by the CDC. The 1990 annual report provided the cumulative safety experience with this vaccine since 1970 for 10,414 doses administered. (This includes 2,203 doses of the vaccine that were administered during the 5 years prior to operation Desert Shield). Available information indicated that individuals could experience side effects associated with vaccination, predominately at the injection site. Such local effects included pain, tenderness, swelling, redness and itching. Systemic reactions such as fever, tiredness, headache, and/or muscle pain could also occur. Rarely an individual could be unable to perform duties for a day or two. Sometimes a lump developed at the injection site which resolved, generally within several weeks. These reactions were described in the information sheet prepared for vaccines in the Desert Storm/Shield protocol.

The experience under this IND provided adequate safety information for the use proposed by DoD. Military clinical

investigators had considerable experience with the use of this vaccine under the IND sponsored by the CDC and were familiar with it's reactogenicity profile. The vaccine dose, route of administration, and schedule in the Desert Storm protocol was identical to that used in the CDC protocol.

This vaccine continues to be used under the CDC's IND. The 1993 annual report to the IND summarizes the cumulative experience of 12,499 doses administered.

The botulinum toxoid vaccine used in the Desert Storm/Shield protocol was manufactured at the Michigan Department of Public Health (MDPH). For this vaccine, the animal testing results for immunogenicity (antibody as determined by a toxin neutralization assay), safety, purity, identity, and sterility for all lots to be used in Desert Storm had been previously reviewed by the Agency and were considered satisfactory for human use. This lot testing is typical for a biological investigational product and could be considered "required" testing prior to the first use of a lot in humans. In addition, results from standardized studies that evaluated animal protection from toxin challenge were available for most of the final lots. Vaccine manufactured at MDPH had been previously tested in humans and was demonstrated to be immunogenic. Some sera from the vaccinated humans in ongoing studies was assessed for ability to neutralize toxin.

The immunogenicity/neutralization and challenge/protection data in animals and the immunogenicity/neutralization data from human studies give evidence of probable effectiveness in humans and have been provided to the Committee. These animal and human data also provide evidence of product safety.

FDA Process

To provide a context for the decision-making process on the use of these two products under these circumstances, the following information is provided.

The Food and Drug Administration (FDA) regulates the use of investigational drugs under provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). In FDA terms, any drug not approved for marketing and any drug used for treatment other than that identified in the approved labeling, is investigational. In order for clinical testing to proceed with unapproved products (or, in some cases, for testing approved products for unapproved uses), an investigational new drug (IND) application is filed with FDA. The IND must contain information sufficient to demonstrate that it is reasonably safe to study the drug in humans, including drug composition, manufacturing and control data, the results of animal and, if available, prior human testing, and the protocol for the planned study. The

investigator must agree to obtain approval of an institutional review board before proceeding, must obtain written informed consent from patients, and must report adverse effects that occur.

The FD&C Act specifically requires that investigators inform subjects receiving drugs under an IND that the drugs are investigational and "obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgment, contrary to the best interests of such human beings." There have been few instances in which obtaining informed consent has not been considered feasible or contrary to patients' interests.

During the months preceding the Persian Gulf War, DoD had discussions with FDA regarding the potential use of specific investigational products in military personnel serving in the Persian Gulf. We also had extensive internal discussions involving technical and policy-level staff, as well as experts from other Federal agencies and academia. It was thought that the products discussed represented the best preventive or therapeutic treatment for diseases endemic to the area in providing protection against possible chemical or biological weapons. DoD requested the assistance of FDA in allowing the use of these products in certain battlefield or combat-related situations in which they considered obtaining informed consent

"not feasible." It should be appreciated that FDA appropriately gave considerable deference to the Department of Defense's judgment and expertise regarding the feasibility of obtaining informed consent under battlefield conditions.

In response to this request, on December 21, 1990, FDA published an interim regulation amending its current informed consent regulations. This regulation allowed the Commissioner of FDA to determine, upon receipt of an appropriate application from DoD, that obtaining informed consent from military personnel for use of a specific investigational drug or biologic would not be feasible in certain circumstances, and to grant a waiver from the requirement for obtaining such consent.

The exception extended, on a case-by-case basis, only to investigational drugs (including antibiotic and biological products) for use in a specific military operation involving combat or the immediate threat of combat. The application was to include the justification for the conclusion (made by physicians responsible for the medical care of the military personnel involved) that: 1) the use was required to facilitate the accomplishment of the military mission, 2) the use would preserve the health of the individuals and the safety of other personnel, without regard for any individual's preference for alternate treatment or no treatment; and 3) the application contained documentation to indicate that the protocol had been reviewed and

approved by a duly constituted institutional review board for the use of the investigational drug without informed consent.

Each application for waiver from the informed consent requirements was assessed by the appropriate FDA review division, and by the agency's Informed Consent Waiver Review Group (ICWRG). The ICWRG included senior management of the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Office of General Counsel, the Office of Health Affairs, and NIH's Office of Protection from Research Risks. This ICWRG core was supplemented by technical experts as appropriate for the particular investigational drug being considered for exception. The ICWRG considered DoD's justification supporting the request for the waiver and the reviewing division's evaluation of the available safety and efficacy data. The ICWRG requested additional supporting information in some cases, and required changes in the information to be provided to the troops in several rounds of iterative exchanges with DoD. The ICWRG then made a recommendation to the Commissioner regarding whether or not to grant the waiver. The Commissioner made a decision on the application, and informed DoD in writing.

IND Requirements

The IND regulations set forth certain regulatory responsibilities for sponsors of INDs, many of which apply to DoD's use of pyridostigmine and botulinum toxoid vaccine. FDA expects IND sponsors to fulfill commitments that are made regarding the conduct of studies. The Agency does not routinely follow up each agreement made with sponsors with respect to drugs being used under an IND. We would, of course, pursue such information if we had reason to believe agreed-upon procedures were not being followed.

The IND requirements include the selection of qualified investigators to conduct and monitor the study, maintenance and retention of records by individual investigators, and submission of progress reports by the investigators. In addition, the sponsor is required to submit safety reports identifying any adverse experience associated with the use of the drug, provide investigators with a brochure containing information on the drug under study, maintain records with regard to the disposition of unused supplies of the drug, and submit annual reports to the IND.

FDA recognized the limitations of these requirements for data collection and recordkeeping under the special circumstances encountered in battlefield conditions. Accordingly, FDA waived

the regulations that apply to the performance and responsibilities of individual investigators because "individual investigators" were not identified in this instance. Certain information was nonetheless required. With regard to the botulinum toxoid vaccine, each vaccination was to be recorded on the individual's permanent immunization record. In addition, a roster was to be maintained with the name, social security number, date and military unit of all individuals receiving each vaccine dose. Adverse reactions were to be reported to the principal investigator. Individuals were specifically advised in the information to be given them to report to sick call if they were worried about a reaction following vaccination. In addition, the sponsor was obligated to perform a post-card survey of at least 100 individuals following vaccination. Under the IND for pyridostigmine, DoD specifically proposed to collect, and summarize, adverse reaction data from medical personnel caring for casualties by the use of a form designed for this purpose, which the Agency found to be acceptable.

Ordinarily, sponsors of INDs are required, among other responsibilities, to report adverse reactions to the FDA in the form of safety reports. The regulations impose different reporting requirements depending upon the seriousness of the reactions. Because of the exigencies of battlefield conditions, the Agency agreed to waive the requirements for the reporting of unexpected fatal or life-threatening experiences by telephone

within 3 days of the receipt of this information by DoD, as well as the requirement for submission, in writing, of reports of reactions that are both serious and unexpected within 10 days of the receipt of this information by DoD. DoD was asked, however, to collect, review, and make reports of all adverse clinical consequences attributed to the treatment in as timely a manner as conditions permitted. In addition, annual reports of experience gained under the IND also were required.

Although it had been concluded that informed consent was not feasible, FDA did obtain DoD's agreement to provide accurate, fair, and balanced information to those who would receive the investigational products. To do this, information leaflets on both products were developed and approved by FDA.

Conclusion

As mentioned above, waivers were granted for two products during Operation Desert Storm/Shield. The regulation allowing informed consent to be waived during this operation was developed to allow what was believed to be the best available medical treatment or preventive therapy to be utilized under combat conditions. FDA granted these waivers because there was reason to believe the products would be effective, because there was no available satisfactory alternative therapy, and because the products appeared safe for the intended use.