ADDRESSES: Secretary to the Board, Railroad Retirement Board, 844 North Rush Street, Chicago, Illinois 60611.

FOR FURTHER INFORMATION CONTACT: Thomas W. Sadler, Senior Attorney, Railroad Retirement Board, 844 North Rush Street, Chicago, Illinois 60611, telephone (312) 751–4513, TTD (312) 751–4701.

SUPPLEMENTARY INFORMATION: Part 295 describes the Board's requirements for obtaining an enforceable order directing the Board to partition a railroad retirement annuity incident to a divorce, settlement, or annulment. Section 295.1(b) describes what benefits are subject to division under this part. Section 295.5(e)(1) further defines the net amount of benefits subject to division as excluding amounts deducted for an employee's elected Medicare Part B premium. When § 295.5(e)(1) was initially approved in 1986, the Board was concerned about the risk that Medicare premium deductions might not be satisfied from the nondivisible portion of an employee's annuity in the event that the portion would not be payable due to work deductions. In practice, however, the agency has determined that only in rare cases is the nondivisible portion insufficient to accommodate the Medicare Part B deduction. The Medicare Part B premium is a personal expense elected to be made by the employee. The Board believes that it is more consistent with the nature of the Part B premium that it be paid entirely by the employee rather than, in effect, partly by the employee and partly by the divorced spouse. Accordingly, the agency proposes that the Medicare Part B deduction need not be deducted from the divisible benefits prior to partition in an action for divorce, settlement, or annulment.

The Board, with the concurrence of the Office of Management and Budget, has determined that this is not a significant regulatory action under Executive Order 12866; therefore, no regulatory impact analysis is required. There are no information collections associated with this rule.

List of Subjects in 20 CFR Part 295

Railroad employees, Railroad retirement.

For the reasons set out in the preamble, chapter II of title 20 of the Code of Federal Regulations is proposed to be amended as follows:

PART 295—PAYMENTS PURSUANT TO COURT DECREE OR COURT-APPROVED PROPERTY SETTLEMENT

1. The authority for part 295 continues to read as follows:

Authority: 45 U.S.C. 231f; 45 U.S.C. 231m.

§ 295.5 [Amended]

2. Section 295.5(e)(1) is amended by removing the comma after ''Board'' and by removing ''and the amount of any Medicare Part B premium''.

Dated: July 24, 1997.

By authority of the Board.

Beatrice Ezerski,

Secretary to the Board.

[FR Doc. 97–20206 Filed 7–30–97; 8:45 am]

BILLING CODE 7905–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 50

[Docket No. 90N–0302]

Accessibility to New Drugs for Use in Military and Civilian Exigencies When Traditional Human Efficacy Studies Are Not Feasible; Determination Under the Interim Rule That Informed Consent Is Not Feasible for Military Exigencies; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Request for comments.

SUMMARY: The Food and Drug Administration (FDA) is requesting written comments related to the advisability of revoking or amending the interim final rule that permitted the Commissioner of Food and Drugs (the Commissioner) to determine that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain situations related to military combat. The agency is also soliciting written comments identifying the evidence needed to demonstrate safety and effectiveness for such investigational drugs that cannot ethically be tested on humans for purposes of determining their efficacy. FDA is seeking written comments from all interested parties, including, but not limited to: Consumers, patient groups, veterans and veteran groups, active-duty military personnel, organizations and departments, ethicists, scientists, researchers with particular expertise in this area, and health care professionals. The written comments are intended to provide FDA with information to help the agency in making policy decisions on the use of investigational products during military exigencies and the appropriate evidence needed to demonstrate safety and effectiveness for drug and biological products used in military or other exigencies when traditional human efficacy studies are not feasible.

DATES: Submit written comments by October 29, 1997.

ADDRESSES: Submit written comments on the questions identified in section II of this document (specifically referencing the number of the question(s) being addressed) to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Bonnie M. Lee, Office of the Executive Secretariat (HF–40), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4450.

SUPPLEMENTARY INFORMATION:

I. Background

There will continue to be military combat situations in which there will be a threat to U.S. military personnel from the possible use of chemical and biological weapons. The Department of Defense (DOD), therefore, has a legitimate interest in protecting military personnel by using products which may provide protection from such chemical and biological agents. In order to support this interest of DOD, FDA issued an interim rule during the Persian Gulf War that permitted DOD to use specified investigational products intended to provide potential protection against chemical and biological warfare agents without obtaining informed consent. A copy of the interim rule that published in the **Federal Register** of December 21, 1990 (55 FR 52813), can be viewed on FDA's website at http://www.fda.gov.

Specifically, following a request from the DOD, FDA granted waivers from its informed consent requirements for the use of two products in specific protocols in the Persian Gulf War: Pyridostigmine bromide and botulinum toxoid vaccine. FDA recognizes that the interim final rule did not work the way that the agency anticipated it would work; therefore, the agency is seeking broad public input to provide information to help FDA in making policy decisions on the future use of such investigational products and possible efficacy demonstrations for these products.

In order to provide a context for the decisionmaking process on the use of pyridostigmine bromide and the

botulinum toxoid vaccine during the Persian Gulf War, the following information is provided.

A. The Regulatory Process

FDA regulates the use of investigational drugs under provisions of the Federal Food, Drug, and Cosmetic Act (the act). In FDA terms, drugs not approved for marketing and drugs studied for treatment other than that identified in the approved labeling, are 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 reasonable to study the drug in humans, including drug composition, manufacturing and control data, the results of animal studies and, if available, prior human testing, and the protocol for the planned study. The investigator must agree to a number of commitments including obtaining approval of an institutional review board (IRB) before proceeding, obtaining written informed consent from subjects, and reporting adverse effects that occur as specified in the protocol.

The act 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 Gulf. It was thought that the products discussed represented the best preventive or therapeutic treatment for diseases endemic to the area and 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.'' DOD's explanation as to why obtaining informed consent would not be feasible under battlefield conditions included the following:

(1) It is not acceptable from a military standpoint to defer to whatever might be the soldier's personal preference concerning a preventive or therapeutic treatment that might save his life, avoid endangerment of the other personnel in his unit and accomplish the combat mission.

(2) Based on unalterable requirements of the military field commander, it is not an option to excuse a nonconsenting soldier from the military mission.

(3) It would not be defensible militarily, or ethically, to send the soldier unprotected into danger.

(4) Special military exigencies sometimes must supersede normal rights and procedures that apply in the civilian community and, thus, military regulations state that military members may be required to submit to medical care determined necessary to preserve life, alleviate suffering or protect the health of others.

At the time, FDA gave considerable deference to the DOD's judgment and expertise regarding the feasibility of obtaining informed consent under battlefield conditions. Thus, in response to DOD's request, in the **Federal Register** of December 21, 1990 (55 FR 52813), FDA published an interim regulation amending its informed consent regulations at 21 CFR 50.23(d).

B. The Interim Regulation

The interim regulation allowed the Commissioner to determine, upon receipt of an appropriate request 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 applied, 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 regulation requires the request to include: (1) The justification for the conclusion (made by physicians responsible for the medical care of the military personnel involved and the investigators involved) that the use is required to facilitate the accomplishment of the military mission, and 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 (2) a statement that a duly constituted IRB has reviewed and approved the use of the investigational drug without informed consent.

Under the interim rule, the Commissioner may find that informed consent is not feasible (and thus may be waived) ''only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.'' The rule sets forth four additional factors that the Commissioner is to consider in making his determination. These factors are: (1) The extent and strength of the evidence of the safety and efficacy of the drug for the intended use, (2) the context in which the drug will be administered (e.g., battlefield or hospital), (3) the nature of the disease or condition for which the preventive or therapeutic treatment is intended, and (4) the nature of the information to be provided to the recipients of the drug concerning the potential risks and benefits of taking or not taking the drug. A determination by the Commissioner that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel expires at the end of 1 year, unless renewed at DOD's request, or when DOD informs the Commissioner that the specific military operation creating the need for the use of the investigational drug has ended, whichever is earlier. In addition, when the Commissioner has issued a waiver to DOD, he may revoke the waiver based on changed circumstances.

The appropriate FDA review division and the Informed Consent Waiver Review Group (ICWRG) assessed each request for waiver from the informed consent requirements. The ICWRG included senior management of FDA and the National Institutes of Health's Office of Protection from Research Risks, supplemented by technical agency 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 identified changes needed in the information to be provided to the troops. The ICWRG then made a recommendation to the Commissioner regarding whether or not to grant the waiver. The Commissioner made a decision on the request and informed DOD in writing.

On December 28, 1990, DOD submitted protocols under IND's and requests for waiver of informed consent for pyridostigmine bromide 30-milligram (mg) tablets and botulinum toxoid vaccine. (Subsequently, DOD submitted a waiver request for multishield topical skin protectant, but later withdrew this request.) Pyridostigmine bromide was considered

a potentially useful pretreatment against certain nerve gases; botulinum toxoid vaccine is widely accepted as offering protection against toxins produced by *Clostridium Botulinum*, the bacterium that causes botulism.

The Commissioner approved DOD's waiver requests for pyridostigmine bromide 30-mg tablets and botulinum toxoid vaccine on December 31, 1990, and January 8, 1991, respectively. Both products were administered to portions of the military personnel who participated in Operation Desert Storm.

Following the cessation of combat activities, the Assistant Secretary of Defense (Health Affairs) notified the Commissioner in a letter dated March 15, 1991, that DOD considered the two waivers granted under the interim rule to be no longer in effect. He also informed the Commissioner that DOD had ultimately decided to administer the botulinum toxoid on a voluntary basis.

C. Comments Received on the Interim Rule

Twenty-two written comments were submitted to the agency in the brief 30-day comment period following publication of the interim rule in the **Federal Register** of December 21, 1990. Comments were received from physicians, members of IRB's, organizations concerned with bioethical issues, patient advocacy groups, and private citizens. The majority of the comments were supportive of the rule, although often with some qualification or suggested change. However, a number of comments expressed vehement opposition to the interim rule, both on general principle and with regard to one or more of its provisions. For example, one comment stated that the request for waiver of informed consent is merely an expedient solution to a problem that should be solved much better in other ways. This comment suggested that FDA modify its drug approval process so that therapies such as those that were sanctioned for use under the interim rule could be granted marketing approval notwithstanding the absence of substantial evidence of their effectiveness against nerve gas or biological warfare agents. Several comments stated that the interim regulation did not provide for recipients of investigational therapies to receive appropriate information on the treatment to be administered. Two comments stated that the interim rule should be modified to require that the reviewing IRB be unaffiliated with DOD. Five comments stated that the interim rule is a violation of fundamental ethical principles. The comments described the rule as ''* * * a flagrantly immoral violation of human rights,'' adding that ''Wartime does not justify experimentation without consent,'' and ''No explanation, whatever it might be, is acceptable to justify these actions.''

D. Summary of Litigation Regarding the Interim Rule

On January 11, 1991, Public Citizen Health Research Group filed suit against the Department of Health and Human Services in the United States District Court on behalf of an unnamed serviceman stationed in Saudi Arabia, his wife, and all others similarly situated. In the Complaint, the plaintiff (''Doe'') alleged that: (1) The interim rule was outside FDA's statutory authority under the act, (2) DOD's use of unapproved investigational drugs, under the informed consent waiver, could not be reconciled with language in the 1985 Defense Department Authorization Act, and (3) the Government's use of drugs on unconsenting persons was a deprivation of liberty in violation of the Fifth Amendment. The district court dismissed the Complaint holding that the Complaint questioned ''a military decision that is not subject to judicial review.'' (*Doe* v. *Sullivan*, 756 F. Supp. 12, 14 (D.D.C. 1991)). In an alternative holding, the district court also rejected on the merits the statutory and constitutional challenges stated in the complaint.

On appeal, a three-judge panel of the United States Court of Appeals for the District of Columbia Circuit affirmed by a two-to-one vote the district court's order dismissing the Complaint on the grounds that FDA's rule was within FDA's authority, and not barred by the 1985 Department of Defense Authorization Act or the due process clause of the Fifth Amendment. The dissenting judge was of the opinion that the case was moot.

E. DOD's Experience With Pyridostigmine Bromide and Botulinum Toxoid

Following the approval of the waiver requests, DOD dispensed pyridostigmine bromide tablets and administered botulinumtoxoid to U.S. troops involved in Operations Desert Shield and Desert Storm who were deemed to be at high risk for exposure to organophosphorus nerve agents or bacterial agents. As part of the legal requirements for the use of products under an IND, DOD was required to collect data on the safety and efficacy of the two agents. This information is summarized as follows:

1. Safety Data on Pyridostigmine

U.S. troops who were deemed to be at high risk for exposure to organophosphorus nerve agents received pyridostigmine bromide tablet packages for self-administration use when ordered to take them as prophylaxis against nerve agents. Unit commanders had discretion on whether, and when, to order use of the pyridostigmine bromide, and could delegate this authority to the lowest level of field command. Documentation does not exist on how far down the command chain the authority was delegated in each unit, or whether or when each unit issued orders to begin taking the pyridostigmine, or who took pyridostigmine.

The Department of the Army conducted three separate surveys in an effort to determine the incidence and severity of side effects associated with the use of pyridostigmine bromide as a nerve agent pretreatment.

Survey I was a questionnaire sent to 42 selected medical personnel involved in Operation Desert Shield and Operation Desert Storm; 23 of these questionnaires were completed and returned. Among the 23 medical officers who returned the survey, 10 responded that their overall impression was that the drug was tolerated either very well or well. The most common side effects reported were gastrointestinal (abdominal cramps, nausea, and diarrhea). Less common side effects were weakness and light-headedness, exacerbation of asthmatic symptoms, fatigue, sleep disturbances, and reduced mental concentration. Of the 5,825 medical personnel reported on, 8 were hospitalized for side effects that were attributed to pyridostigmine. The reasons listed for hospitalization included exacerbation of cholelithiasis, asthma, and allergic skin reaction.

Survey II was a questionnaire given to an unspecified number of soldiers deployed in Operation Desert Storm; 149 of these soldiers responded. Of those individuals who took the drug, 37.5 percent experienced side effects. The most common side effects were gastrointestinal in nature. Nausea was reported most frequently (11 percent of subjects), and headache was the second most frequent side effect reported (7.5 percent of subjects).

Survey III was designed to document the effects of pyridostigmine on aviators' ability to carry out combat missions. One hundred eighteen aviators participated in the survey, 48 of whom were taking other medications concomitantly. The majority of those taking other medications were taking

the antibiotic ciprofloxacin. Twenty-six of the 108 aviators who indicated that they had taken the drug reported experiencing side effects they attributed to pyridostigmine, mainly headaches and diarrhea.

The *Journal of the American Medical Association* published the result of one retrospective study that reported on the 18th Airborne Corps (Corps) use of pyridostigmine. The Corps instructed 41,650 soldiers (6.5 percent women) to take pyridostigmine at the beginning of Operation Desert storm in January 1991. Approximately 30 medical officers (physicians and physician's assistants) provided their impressions of the incidence of physiologic responses and potential adverse effects to pyridostigmine. A total of 483 aid station or clinic visits were related to pyridostigmine administration; 313 of these visits were due to ''gastrointestinal disturbances severe enough to prompt medical attention.'' And ''[a]nother 150 soldiers had frequency or urgency of urination.'' Less than 5 percent of the 41,650 soldiers complained of headaches, rhinorrhea, diaphoresis, or tingling of extremities. The article reported that 1 percent of the troops perceived the need for a medical visit and less than 0.1 percent discontinued pyridostigmine based on medical advice (LTC Jill R. Keeler, et al., ''Pyridostigmine Used as a Nerve Agent Pretreatment Under Wartime Conditions,'' *Journal of the American Medical Association*, vol. 266, no. 5, August 7, 1991).

2. Safety and Efficacy Data on Botulinum Toxoid Vaccine

As noted previously, DOD advised FDA that the military command in the theater of operations administered this vaccine on a voluntary basis. Approximately 8,000 service members were reported to have received the botulinum toxoid vaccine. Most of these individuals received two doses.

The Department of the Army collected safety information through a retrospective survey on local and generalized reactions experienced by soldiers vaccinated with the botulinum toxoid vaccine. The survey, conducted on August 27, 1991, was given to individuals who received one or more doses of the vaccine (between January 3, 1991, and March 2, 1991) in the Persian Gulf, and who had received no other vaccines against biological warfare agents. One hundred and twenty-one responses were received. With respect to local reactions, 84 percent of vaccinated individuals reported either no local reactions (72.5 percent) or redness and/or swelling less than 6 inches in any dimension (11.57 percent). One individual reported post-vaccination injection site pain that temporarily (one half day) interfered with his ability to perform his duties but resolved quickly. With respect to systemic reactions to the vaccine, 97.52 percent of respondents reported having none. Of the three respondents who reported systemic reactions, two reported mild systemic effects such as headache and muscle aches, and the third also reported nausea, fever, and fatigue; none of these events were reported to have persisted or have resulted in limitations on activity.

In 1992, DOD carried out a followup study, with informed consent, on 327 selected military personnel who received the botulinum toxoid vaccine during Operation Desert Shield and Operation Desert Storm. The objectives of this study were, in part, to evaluate the persistence of antibodies to botulinum toxoid vaccine received during the Gulf War and, to determine the serological response 30 days after a booster dose. The evaluation demonstrated that 35 of the 327 had measurable antibody 18 to 24 months following primary vaccination. The percentage of antibody varied depending on whether the individuals had received 1, 2, or 3 primary vaccinations ((0/10 (0 percent), 27/244 (11.1 percent), and 8/73 (11 percent) of individuals who had received 1, 2, or 3 primary vaccinations, respectively). This response was to be expected at this followup time point in individuals receiving anything less than the full primary immunization and booster dose. Thirty days after the booster dose was administered, 7/10 (70 percent), 238/244 (97.5 percent), and 72/72 (98.6 percent) of individuals who had received 1, 2, or 3 of the primary dose series, respectively, responded with a significant increase in toxin neutralizing antibody titer to botulinum type A.

3. Information Supplied to Military Personnel

DOD has stated that its implementation of plans for providing service members with information about the investigational products was frustrated due to time limitations.

In order to evaluate the effectiveness of its efforts to disseminate information to military personnel regarding the safety, risks, and possible benefits of pyridostigmine, the Army surveyed an unspecified number of personnel regarding their views on the adequacy of the information that they received. This was a part of Survey II described in section I.E.1 of this document. Those surveyed were asked whether they thought the training that they received was adequate and to comment about any problems with their training.

One hundred forty-nine individuals responded to this survey. In response to the question ''Was training about pyridostigmine adequate?'', 43.7 percent of the respondents answered in the negative. Most of those who felt that the training was inadequate expressed a desire for more information on side effects, long-term effects, and the drug's mechanism of action. The following is a sample of some of the comments received (both by those who felt the training was inadequate and those who felt it was adequate but could have been better):

(a) ''No standard side effects given.''

(b) ''No training on side effects.''

(c) ''People were worried about the drug's side effects. Many people avoided taking it. Some people would double dose after missing one.''

(d) ''Not trained on drug action, but yes on side effects.''

(e) ''Combat lifesavers brief it and said it was FDA approved.''

(f) ''Many soldiers didn't take the tablets due to the fact that they weren't FDA approved or thought not.''

(g) ''Didn't know what it did, what it was for. Disregarded instructions to take it.''

(h) ''Training was not enough in layman's terms. You would need to know more about nerve agents.''

Veterans made similar comments on the adequacy of the information they received at hearings before the Senate Committee on Veterans' Affairs and the Presidential Advisory Committee on Gulf War Veterans' Illnesses.

As part of Survey I described in section I.E.1 of this document, 15 of the 23 medical officers who returned the survey responded that to their knowledge, the information sheet on pyridostigmine bromide was not distributed to personnel instructed to take pyridostigmine bromide. Two respondents said that the information was distributed, and one respondent, whose unit was not instructed to begin pretreatment with pyridostigmine bromide, replied that he had the sheet available for distribution.

Although FDA did not require the Army to attempt to evaluate the effectiveness of its educational efforts, the Army did so in an effort to monitor its own performance and perhaps learn about how education might be improved in the future. While it is difficult to evaluate the validity of the Army's findings (due to the difficulty of measuring the effect of response bias in Survey II), FDA is concerned about the high level of dissatisfaction expressed

by this small sample of military personnel. Their responses indicate that the information on pyridostigmine was not distributed as intended and the Army's educational activities were uneven and possibly inappropriate to the education level of all personnel. Their responses also indicate that because of the inadequate information provided to the soldiers, that at least some soldiers either took the wrong amount of pyridostigmine or disregarded orders to take it completely. Based on subsequent DOD statements, FDA has concluded that the information sheet on pyridostigmine was not provided and disseminated to military personnel in the Gulf as conditioned in the Commissioner's letter granting the waiver under the interim rule.

With respect to botulinum toxoid vaccine, there is a lack of clarity as to whether the conditions of waiver were met and applied or whether informed consent was actually obtained.

F. Other Information Related to the Interim Rule

There has been extensive examination of the use of the interim rule, pyridostigmine bromide, and the botulinum toxoid vaccine during Operation Desert Storm. This focused examination is, in part, the result of interest in determining the cause of a variety of health effects suffered by veterans who served in the Gulf War.

On May 6, 1994, the United States Senate Committee on Veterans' Affairs held a hearing on ''Is Military Research Hazardous to Veterans' Health? Lessons From World War II, the Persian Gulf, and Today.'' The Chairman, in his opening statement, stated his view that the issue needed to be resolved. Witnesses at the hearing included ethicists, four veterans with stories of illnesses allegedly related to exposures they experienced either in the military or working for the military, and scientists and officials from the Department of Veterans Affairs, DOD, FDA, and the Department of Agriculture.

The Presidential Advisory Committee on Gulf War Veterans' Illnesses' final report reviewed these issues extensively. In its interim report (February 1996), the committee described a number of shortcomings in DOD's use of investigational products during the Gulf War and recommended, among other things, that:

If FDA decides to reissue the interim final rule as final, it should first issue a Notice of Proposed Rule Making. Among the areas that specifically should be revisited are: adequacy of disclosure to service personnel; adequacy of recordkeeping; long term followup of individuals who receive investigational products; review by an IRB outside of DOD; and additional procedures to enhance understanding, oversight, and accountability. (p. 24)

This report further stated:

The activities of FDA and DOD related to the use of drugs and biologics intended to protect against [chemical and biological warfare] CBW remain an area of considerable interest to the Committee. In particular, we plan to explore with FDA possible alternatives to the interim final rule to help ensure troops are protected against CBW. Some observers have suggested an approval standard that recognizes surrogate endpoints and other data indicative of efficacy for vaccines, drugs, devices, and antibiotics intended for CBW defense might be a more appropriate policy than a waiver of informed consent. (p. 44)

On May 7, 1996, Public Citizen, the National Veterans Legal Services Program, and the National Gulf War Resource Center, Inc., submitted a petition to FDA requesting that the Commissioner repeal the interim rule. The petition set forth a number of grounds for this request, including: The ethics of the rule continues to be questioned; the military did not provide the information regarding the effects of experimental drugs that FDA considered essential to permitting their use without informed consent; DOD failed to keep the necessary records on the administration and effects of the experimental drugs; the waiver of informed consent was not necessary (botulinum toxoid vaccine was ordered to be given on a voluntary basis and ''the fact that the PB tablets were self-administered by the troops underscores that it was possible to inform and obtain the consent of the military personnel who took these tablets''); the safety of the experimental drugs is still questionable; and administration of these drugs without informed consent was not limited to military personnel.

The petition concluded with the following:

The FDA should repeal the Interim Rule in light of all the problems encountered in its implementation. Not only did the Interim Rule fail to operate in the manner the FDA intended, but it also allowed the military to circumvent the safeguards the FDA offered to rationalize this departure from its ordinary rules on informed consent. The military did not follow through with many conditions that the FDA deemed crucial to granting a waiver of this critical requirement. (p. 26)

On September 13, 1996, the Assistant Secretary of Defense, Health Affairs, provided DOD's comments on the petition to FDA and urged that it be denied. DOD's comments included the following statements:

1. When the President commits U.S. military forces to a combat, peacekeeping, or humanitarian deployment, the U.S. Government has a duty to take all reasonable precautions to bring about a successful completion of the mission and a safe return of the deployed forces.

2. The Government's duty to take all reasonable precautions to preserve the fighting force must include recognition of the startling proliferation of chemical and biological weapons among potential adversaries and terrorist organizations and an obligation to implement the best possible medical countermeasures.

3. Implementation of the best possible medical countermeasures may require the standardized treatment use of an investigational new drug or vaccine for all personnel at risk in a military combat exigency, including those personnel who, for whatever reason or no reason at all, would prefer an alternate treatment or no treatment.

4. The current rule is an extremely limited authority, requiring case-by-case justification, available only under extraordinary circumstances, and explicitly restricted to advancing the best interests of the military personnel concerned.

5. The current rule is fully consistent with law and ethics.

6. Overall, notwithstanding some problems in carrying out the designed treatment protocols, the two uses made of the current rule during the Persian Gulf War support the rule's continuation.

7. Initiatives since the Gulf War, including current operations in Bosnia, have improved DOD's ability to implement medical countermeasures under the authority of the current rule, should that become necessary in the future.

This petition is pending before the agency.

II. Scope of Comments Requested

In light of the many complex ethical, scientific, and public health issues associated with the use of investigational products during the Gulf War and the waiver of the requirement to obtain informed consent, FDA is soliciting broad public comment on the advisability of the agency: (1) Revoking or amending the interim final rule that permits the Commissioner to determine that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain situations related to military combat, and (2) identifying the evidence needed to demonstrate safety and effectiveness for such investigational drugs that cannot ethically be tested on humans for purposes of determining their efficacy because they would involve administering a severely toxic substance to human volunteers. The agency encourages written comments from all interested parties, including, but not limited to, consumers, patient groups, veterans and veteran groups, active military personnel, organizations and departments, ethicists, scientists,

researchers with particular expertise in this area, and health care professionals.

Interested persons may, on or before October 29, 1997, submit to the Dockets Management Branch (address above) written comments regarding the questions identified in section II of this document (referencing the number of the question(s) being addressed). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The agency specifically requests comments on the following:

A. The Interim Rule

(1) Should the agency revoke the interim rule? If so, why?

(2) Are there circumstances under which use of the interim rule would be justified? If so, what are those circumstances?

(3) The interim rule is based on the premise that informed consent is not feasible in military combat exigencies because if a soldier were permitted to say ''no,'' this could jeopardize the individual soldier's life, endanger other personnel in his or her unit, and jeopardize the accomplishment of the combat mission. DOD has alleged that it is not an option to excuse a nonconsenting soldier from a military mission. Given the experience in the Gulf War, does this rationale still hold?

(4) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent from military personnel during peace time for the future use of investigational products during a military conflict? If it is feasible, would such consent be valid as ''informed consent''? What would be the needed consent algorithm to make it valid and feasible?

(5) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent from military recruits (prior to their recruitment into the military) for the future use of investigational products during a military conflict? If it is feasible, would such consent be valid? What would be the needed consent algorithm to make it valid and feasible?

(6) If the interim rule is needed, are there changes that should be made to it based on experiences during and following the Gulf War? If so, what are these changes and why should they be made?

(7) Can or should the interim rule be narrowed in scope? If so, how?

(8) If the rule were to be reproposed:

(a) Should there be a requirement that DOD's proposed use of the investigational product(s) be approved by an IRB that is independent of DOD? If so, why should DOD be held to a requirement not imposed on other institutions, and what should be the requirement for that independent IRB? Can this be accomplished without compromising military or national security?

(b) Should the authority to make the ''feasibility determination'' (i.e., whether obtaining informed consent is ''not feasible'') under the interim rule be vested in persons or entities other than the Commissioner of FDA?

(c) Should the rule be more specific in describing the information that must be supplied to military personnel, or should FDA have wide latitude to make such determinations on a case-by-case basis?

(d) Should additional measures be taken to insure that information required by FDA is effectively conveyed to the affected military personnel? If so, what should these measures be?

(e) Should the rule address what constitutes adequate recordkeeping and adequate long term followup of individuals who receive investigational products? If so, in what way?

(f) Should the rule contain additional procedures to enhance understanding, oversight, and accountability? If so, what are these procedures?

(g) Should the rule contain additional procedures to track noncompliance?

B. When Is It Ethical to Expose Volunteers to Toxic Chemical and Biological Agents to Test the Effectiveness of Products That May Be Used to Provide Potential Protection Against Those Agents?

The agency recognizes that reliance on nonhuman studies will almost always give greater uncertainty about effectiveness than would studies in humans. Therefore, the agency is also seeking comments on the ethical and scientific considerations of conducting human efficacy trials with these products. For example, the agency is interested in receiving comment on whether it is ethical to conduct challenge studies in humans if, should the test product fail, there is strong reason to believe the effect of the challenge could be reversed or effectively treated. What if the effect of the challenge could not be reversed or effectively treated? What would be the needed risk/benefit assessment? Who could volunteer for such studies? Would it be ethically preferable to carry out such studies in people who could be exposed to the toxic substance? Should the agency further explore these issues in a separate public forum?

C. If Products That May Be Used to Provide Potential Protection Against Toxic Chemical and Biological Agents Cannot Be Ethically Tested in Humans, What Evidence Would Be Needed to Demonstrate Their Safety and Effectiveness?

(1) Should FDA identify the evidence needed to demonstrate safety and effectiveness for drugs that cannot ethically be tested on humans to demonstrate efficacy when such tests would involve administering a severely toxic substance to human volunteers? If ''yes,'' what should constitute the evidence needed to demonstrate safety and efficacy? (The current statutory standard requires, among other things, there be ''substantial evidence'' that the drug is effective; ''substantial evidence'' means evidence ''consisting of adequate and well-controlled investigations, including clinical investigations * * * on the basis of which it could fairly and responsibly be concluded by such experts that the drug'' is effective.)

(2) If the agency were to identify the evidence needed to demonstrate safety and effectiveness of these products, would this preclude the need for the interim rule? What specific advantages would this offer over the interim rule?

(3) Civilian populations may require products used in the prevention or treatment of the serious or life-threatening effects from exposure to toxic chemical or biological agents, e.g., in the event of exigencies such as the release of toxic chemical agents in the Tokyo subway system. Thus, should the agency consider identifying the evidence needed to demonstrate safety and effectiveness for these products which would apply to both civilian as well as military populations?

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Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

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