

# **federal register**

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## **Part VII**

# **Department of Health and Human Services**

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**Food and Drug Administration**

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**21 CFR Part 50**

**Informed Consent for Human Drugs and  
Biologics; Determination That Informed  
Consent Is Not Feasible; Interim Rule  
and Opportunity for Public Comment**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****Food and Drug Administration****21 CFR Part 50**

[Docket No. 90N-0302]

**Informed Consent for Human Drugs and Biologics; Determination That Informed Consent Is Not Feasible****AGENCY:** Food and Drug Administration, HHS.**ACTION:** Interim rule: opportunity for public comment.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing an interim regulation to amend its current informed consent regulations. This will permit the Commissioner of Food and Drugs to make the determination that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain battlefield or combat-related situations. The amendment authorizes the Commissioner to make such a determination when the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) named in the investigational new drug application (IND) provide written justification for their conclusions that, in the use of specific investigational drugs or biologics in a specific combat-related situation, obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of the military personnel because of military combat exigencies and that the waiver of informed consent is ethically justified. Military combat (actual or threatened) circumstances in which the health of the individual or the safety of other military personnel, may require that a particular drug or biologic for prevention or treatment be provided to a specified group of military personnel, without regard to any individual's personal preference for no treatment or for some alternative treatment. The Department of Defense (DOD) must also provide a written statement that the use of the investigational drug or biologic and the waiver of informed consent has been reviewed and approved by a duly constituted institutional review board (IRB). In determining whether obtaining informed consent is not feasible in these circumstances, the Commissioner must also consider certain other criteria. This action is being issued as an interim rule with an immediate effective date because of the urgency created by current military operations in Operation Desert Shield.

**DATES:** *Effective date:* Interim rule effective December 21, 1990. *Comment date:* Comments must be received by January 22, 1991.

**ADDRESSES:** Written comments to the Dockets Management Branch (HFA-3051, Food and Drug Administration, room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Allen Duncan, Office of Health Affairs (HFY-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-6143.

**SUPPLEMENTARY INFORMATION:****I. Informed Consent Regulations**

Sections 505(i) and 507(d) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i) and 357(d)) require FDA to publish regulations governing the use of human drugs, including certain biologics and antibiotics, in clinical investigations (hereafter "investigational drugs"). Sections 505(i) and 507(d) provide that such regulations must include, among other requirements, a requirement that investigators who use investigational drugs inform the subjects of their investigations 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."

FDA issued its current regulations governing informed consent in the **Federal Register** of January 27, 1981 (46 FR 8942). Those regulations, codified in 21 CFR part 50, apply to all clinical investigations regulated by FDA under sections 505(i), 507(d), and 520(g) (21 U.S.C. 360j(g)) of the act, as well as to clinical investigations that support applications for research or marketing permits for products regulated by FDA. The regulations require that investigators obtain informed consent from the subjects of clinical investigations. The only circumstance in the current regulations in which obtaining informed consent is deemed not to be feasible is for emergency use of an investigational article, where both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing that: (1) The subject is confronted by a life-threatening situation necessitating the use of the test article; (2) informed consent cannot be obtained because of an inability to communicate with or obtain legally effective Consent from the subject; (3) there is insufficient time to obtain consent from the subject's legal representative; and (4) there is no

available approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. The current regulations do not permit a determination that obtaining informed consent is otherwise not feasible or is contrary to the best interest of the subject.

**II. DOD's Request**

The Assistant Secretary of Defense (Health Affairs) set forth DOD's request in his October 30, 1990 letter to the Assistant Secretary for Health of the Department of Health and Human Services as follows:

This is to follow up on discussions of DoD and HHS personnel over the past weeks. As you know, the memorandum of understanding between DoD and the Food and Drug Administration recognizes "special DoD requirements to meet national defense considerations." Operation Desert Shield presents such special DoD requirements.

Our contingency planning in Desert Shield has had to take into account endemic diseases in the area and the well-publicized capabilities of the Iraqi military with respect to chemical and biological weapons. For some of these risks, we have determined that the best preventive or therapeutic treatment calls for the use of products now under "investigational new drug" (IND) protocols of the FDA.

These are not exotic new drugs: these drugs have well-established uses (although in contexts somewhat different from our requirements) and are believed by medical personnel in both DoD and FDA to be safe. For example, one product consists of a very commonly used drug packaged in a special intramuscular injector to make it readily useable by soldiers on the battlefield. Another example involves a vaccine long recognized by the Centers for Disease Control as the primary preventive treatment available for a particular disease, but the relative infrequency of its use has slowed the accumulation of sufficient immunogenicity data to yet support full licensing of the product. Still another example involves a drug in common use at a particular dosage level, but to preserve alertness of the soldiers, we prefer a lower-dosage tablet, which is not an FDA approved product. FDA personnel have been extremely cooperative and supportive in reviewing our proposed protocols for these products, quickly providing favorable responses to all of our submissions to date.

FDA assistance is also needed on the issue of informed consent. Under the Federal Food, Drug and Cosmetic Act, the general rule is that, regardless of the character of the medical evidence, any use of an IND whether primarily for investigational purposes or primarily for treatment purposes, must be preceded by obtaining informed consent from the patient. The statute authorizes exceptions, however, when the medical professionals administering the

product "deem it not feasible" to obtain informed consent.

Our planning for Desert Shield contingencies has convinced us that another circumstance should be recognized in the FDA regulation in which it would be consistent with the statute and ethically appropriate for medical professionals to "deem it not feasible" to obtain informed consent of the patient—that circumstance being the existence of military combat exigencies, coupled with a determination that the use of the product is in the best interest of the individual. By the term "military combat exigencies", we mean military combat (actual or threatened) circumstances in which the health of the individual, the safety of other personnel and the accomplishment of the military mission require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment.

In all peacetime applications, we believe strongly in informed consent and its ethical foundations. In peacetime applications, we readily agree to tell military personnel, as provided in FDA's regulations, that research is involved, that there may be risks or discomforts, that participation is voluntary and that refusal to participate will involve no penalty. But military combat is different. If a soldier's life will be endangered by nerve gas, for example, 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. Based on unalterable requirements of the military field commander, it is not an option to excuse a non-consenting soldier from the military mission, nor would it be defensible militarily—or ethically—to send the soldier unprotected into danger.

To those familiar with military command requirements, this is, of course, elementary. It is also very solidly established in law through a number of Supreme Court cases establishing that special military exigencies sometimes must supersede normal rights and procedures that apply in the civilian community. Consistent with this, long-standing 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.

Such special military authority carries with it special responsibility for the well-being of the military personnel involved. Thus, we propose specific procedural limitations on the "not feasible" waiver of informed consent based on military combat exigencies. We propose that decisions on waiving informed consent be made on a case-by-case basis by the Commissioner, assuring an objective review outside of military channels of all pertinent information and an independent validation of the special circumstances presented. Further, we propose the following specific limitations: (1) That drug-by-drug requests for waiver be accompanied by written justification based on the intended

uses and the military circumstances involved; (2) that no satisfactory alternative treatment is available; (3) that available safety and efficacy data support the proposed use of the drug or biologic product; (4) that each such request be approved by the applicable DoD Institutional Review Board; and (5) that the waivers be time-limited.

To recap, we have nothing exotic in the works. We are methodically planning for a range of medical treatment contingencies in Operation Desert Shield corresponding to the predictable medical problems that might arise. Some of these contingencies require the availability of products now under IND protocols. For products that will be in the best interests of the patients, military combat exigencies may justify deeming it not feasible to obtain informed consent. FDA's regulation should provide the mechanism, subject to appropriate limitations, for DOD to request on a drug-by-drug basis, and the Commissioner to decide, that a waiver be granted in cases in which it is established that military combat exigencies make that necessary.

Your cooperation and assistance in this regard is appreciated.

### III. Provisions of This Regulation

FDA continues to recognize its responsibility in protecting the human subjects exposed to investigational drugs and the central role that informed consent plays in ensuring that protection. Because of the paramount importance of informed consent, only the narrowest exceptions to this requirement are consistent with FDA's responsibilities and consistent with the best interests of human subjects. Nevertheless, FDA has determined that, in the special circumstances that may be created by the use of troops in combat and consistent with its obligations under sections 505(i) and 507(d), FDA may narrowly expand the circumstances in which the Commissioner may determine that obtaining informed consent is not feasible. FDA agrees with DOD's judgment that, in certain combat-related situations, it may be appropriate to conclude that obtaining informed consent from military personnel for the use of investigational drugs is not feasible and withholding treatment would be contrary to the best interests of military personnel involved. DOD has the right and responsibility to make command decisions that expose troops to the possibility of combat and has the concomitant responsibility to protect the welfare of these troops both individually and as a group. DOD has stated that traditional informed consent, based on the right of the individual to choose his or her own treatment, may not be appropriate under the circumstances of specific combat-related conditions. FDA respects DOD's obligation and commitment to do everything possible to protect military personnel who may be

exposed to potentially hazardous conditions. FDA further appreciates that this protection may include medical treatment or prevention with an investigational drug considered necessary to protect not only the health of individual soldiers but to ensure the welfare of the remaining forces. FDA will consider investigational products proposed for military use on a case-by-case basis, and the agency is prepared to waive the requirement of informed consent where it can be documented that use of these agents in combat-related situations serves the best interests of individual soldiers and the military combat units in which they serve. Since these individual soldiers may be required to be exposed to combat, permitting them to choose whether to receive an investigational product that is the only available satisfactory protection against life-threatening conditions, is contrary to their individual best interests and to the welfare of the other soldiers involved. FDA therefore believes that such an exercise of the Commissioner's discretion is ethically justified. Moreover, all the products at issue would be reviewed by FDA for safety and expanded availability, and their use would be monitored by DOD and reported to and reviewed by FDA. DOD and FDA do not expect that all combat-related situations will create a situation of the kind that would obviate obtaining informed consent. DOD and FDA must determine that there is justification for a waiver of informed consent for a particular drug, following the approval of the use and the waiver by a duly constituted IRB, and a conclusion that the circumstances surrounding the anticipated distribution and use of the drug meet the limited circumstances recognized in the regulations. DOD and FDA also emphasize that accepted ethical principles permit waiver of informed consent only where the preventive or treatment is in the best interests of the individuals involved. Therefore, it is not sufficient as an ethical matter to waive informed consent in the military context where obtaining informed consent is "not feasible," unless it is also the case that withholding the treatment would be contrary to the best interests of the individuals involved. FDA is therefore amending 21 CFR 50.23 to add limited conditions under which the Commissioner may find that it is not feasible to obtain informed consent in the proposed use of an investigational drug. Under the amended regulation, the Commissioner will make any such determination on a product-by-product

basis. In determining whether obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of the military personnel, the commissioner must find that there is no available satisfactory alternative therapy for the intended diagnosis, prevention, or treatment of the disease or condition. The Commissioner will also consider other factors, including the extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use. Other factors that the Commissioner will consider include the nature of the information provided to the recipients of the investigational drug concerning the potential risks and benefits of the drug, known adverse effects of the drug, and risks of not taking such a product in combat-related situations, whether the disease or condition to be treated is life-threatening or highly contagious and debilitating, and the setting in which the drug is to be administered. For example, it may be more feasible to obtain informed consent in a hospital than on the battlefield or when it is administered by a health professional rather than self-administered. FDA recognizes, however, that there may be combat-related circumstances in which obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel even outside battlefield conditions.

When DOD seeks a determination by FDA that obtaining informed consent would not be feasible in the proposed use of a specific investigational drug and withholding treatment would be contrary to the best interest of the military personnel, DOD must submit a written request. The request must be for use of a specific investigational drug in a specific protocol under an IND sponsored by DOD, in a specific combat-related setting. The request will also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what may be any individual's personal preference for no treatment or for some alternative treatment.

The request must further contain a statement that the duly constituted IRE has reviewed and approved the proposed use of the investigational drug and concluded that it may be administered without obtaining informed consent under the criteria set forth in this document. The request must be submitted with the original IND submission or as an amendment to the IND.

The Commissioner may consult with appropriate experts, including those responsible for the Protection of human subjects, before reaching a determination on a DOD request under this regulation.

To ensure that the Period in which informed consent is not obtained does not exceed that necessary to deal with the actuality or threat of combat, the Commissioner's determination regarding informed consent will automatically expire at the end of 1 year or when DOD informs FDA that the specific military operation creating the need for the investigational drug has ended, whichever is earlier. If, at the end of 1 year, United States military forces are still engaged in the military operations, DOD may seek to renew the determination. This provision does not preclude the Commissioner from revoking or otherwise modifying the determination at any time based upon changed circumstances. In particular, consistent with DOD's responsibilities under the IND's under which these products will be administered, DOD will collect data on any use of these products without informed consent. FDA will review these data and will revoke or modify the determination if the review indicates that the determination is no longer appropriate.

This amendment applies only to the use of investigational drugs. It does not apply to other clinical investigations to which 21 CFR part 50 applies.

#### IV. Effective Date

FDA is issuing this amendment as an interim rule, with an effective date on publication in the **Federal Register** because of the urgent need to provide adequate medical support for Operation Desert Shield, a military operation involving the immediate threat of combat, which is already underway. Because of the unexpected and emergency nature of this situation, and the need for immediate action to meet the requirements of national defense, FDA finds, in accordance with section 553(b) of the Administrative Procedure Act (5 U.S.C. 553(b)(3)(B)), that it would be impracticable and contrary to the public interest to provide for notice and public comment. For these reasons, FDA

also finds, in accordance with section 553(d) of the Administrative Procedure Act (5 U.S.C. 553(d)), that it has good cause to make this rule effective on publication in the **Federal Register** and that this rule relieves a restriction, an independent basis for an immediate effective date under the Administrative Procedure Act. As an additional independent basis for an effective date on publication in the **Federal Register**, this rule involves a military affairs function of the United States within the meaning of section 553(a)(1) of the Administrative Procedure Act (5 U.S.C. 553(a)(1)). FDA is, however, allowing 30 days for public comment on the interim rule in accordance with its procedural regulations (21 CFR 10.40(e)). FDA believes that the same emergency conditions described above justify shortening its usual comment period from 60 to 30 days.

#### V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VI. Economic Impact

The agency has examined the economic impact of this rule and has determined that the rule will not have a significant economic impact on a substantial number of small entities as defined by the Regulatory Flexibility Act (Pub. L. 96-395). In accordance with section 3(g)(1) of Executive Order 12291, the impact of this rule has been analyzed and it has been determined that this final rule is not a major rule as defined in section 1(b) of the Executive Order.

#### List of Subjects in 21 CFR Part 50

Informed consent, Prisoners, Reporting and recordkeeping requirements, Research, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 50 is amended as follows:

#### PART 50—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 continues to read as follows:

**Authority:** Secs. 201, 408, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353,

355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

2. Section 50.23 is amended by adding new paragraph (d) to read as follows:

**§ 50.23 Exception from general requirements.**

\* \* \* \* \*

(d)(1) The Commissioner may also determine that obtaining informed consent is not feasible when the Assistant Secretary of Defense (Health Affairs) requests such a determination in connection with the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD). DOD's request for a determination that obtaining informed consent from military personnel is not feasible must be limited to a specific military operation involving combat or the immediate threat of combat. The request must also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of

the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment. The written request must also include a statement that a duly constituted institutional review board has reviewed and approved the use of the investigational drug without informed consent. The Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.

(2) In reaching a determination under paragraph (d)(1) of this section that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel, the Commissioner will review the request submitted under paragraph (d)(1) of this section and take into account all pertinent factors, including, but not limited to:

(i) The extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use;

(ii) The context in which the drug will be administered, e.g., whether it is intended for use in a battlefield or

hospital setting or whether it will be self-administered or will be administered by a health professional;

(iii) The nature of the disease or condition for which the preventive or therapeutic treatment is intended and

(iv) The nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug.

(3) The Commissioner may request a recommendation from appropriate experts before reaching a determination on a request submitted under paragraph (d)(1) of this section.

(4) 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 will expire 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. The Commissioner may also revoke this determination based on changed circumstances.

**James S. Benson,**

*Deputy Commissioner of Food and Drugs.*

**Louie W. Sullivan,**

*Secretary of Health and Human Services.*

Dated: December 18, 1990.

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