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Human Drugs and Biologics; Determination That Informed Consent Is NOT Feasible or Is Contrary to the Best Interests of Recipients; Revocation of 1990 Interim Final Rule; Establishment of New Interim Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50 and 312

RIN 0910–AA89

[Docket No. 90N–0302]

Human Drugs and Biologics; Determination That Informed Consent Is NOT Feasible or Is Contrary to the Best Interests of Recipients; Revocation of 1990 Interim Final Rule; Establishment of New Interim Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule; opportunity for public comment.

SUMMARY: The Food and Drug Administration (FDA) is revoking its 1990 interim final regulations 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. FDA also is issuing a new interim final rule addressing waiver of informed consent in military operations. FDA is taking these actions based on its analysis and consideration of all relevant facts, including its evaluation of the Department of Defense's (DOD) experience during the Persian Gulf War, its evaluation of the comments received by the agency in response to the agency's July 31, 1997, request for comments on whether the agency should revise or revoke the interim regulations, and the enactment of the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (the Defense Authorization Act). Under the Defense Authorization Act, the President is authorized to waive the Federal Food, Drug, and Cosmetic Act's (the act) informed consent requirements in military operations if the President finds that obtaining consent is infeasible or contrary to the best interests of recipients and on an additional ground that obtaining consent is contrary to national security interests. In light of the enactment of the Defense Authorization Act, with an immediate effective date, and because the President could be called upon to make a waiver determination for military personnel engaged in a specific military operation at any time, the agency believes that it is critical to have in place adequate criteria and standards for the President to apply in making an informed consent waiver determination. Therefore, FDA is issuing a new interim final regulation with an immediate effective date to establish criteria and standards for the President to apply in making a determination that informed consent is not feasible or is contrary to the best interests of the individual recipients.

DATES: Effective October 5, 1999. Submit written comments by December 20, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Bonnie M. Lee, Division of Compliance Policy, Office of Enforcement, Office of Regulatory Affairs (HFC–230), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0415.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is revoking its interim final regulations related to informed consent for human drug and biological products that permitted 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. On a case-by-case basis, the interim final rule authorized the Commissioner to make such a determination at the written request of the Assistant Secretary of Defense (Health Affairs). Any determination made with respect to the nonfeasibility of obtaining informed consent expired at the end of 1 year, unless renewal was requested, or when DOD informed the Commissioner that the military operation had ended, whichever was earlier.

In the **Federal Register** of July 31, 1997 (62 FR 40996), FDA published a document entitled "Request for Comments" that discussed the use of investigational drugs and biologicals in military and other emergency settings to treat or prevent toxicity of chemical or biological substances (hereinafter referred to as the July 1997 request for comments). In this document, FDA provided extensive background on the development and implementation of the 1990 interim rule and DOD's experience during the Persian Gulf War. The agency's request for comments included specific questions in the three following subject areas.

First, the agency asked whether its rule permitting waiver of informed consent in very limited circumstances involving military exigencies should be revoked or amended, and if so, how. In 1990, FDA issued an interim rule ("Informed Consent for Human Drugs and Biologics; Determination that Informed Consent is Not Feasible" (§ 50.23(d) (21 CFR 50.23(d)) (55 FR 52814, December 21, 1990)), allowing the Commissioner to make the determination, in response to product specific requests from DOD, that obtaining informed consent from military personnel for the use of an investigational drug or biological product is not feasible in certain battlefield or combat-related situations.

Second, because information on a product's efficacy in reducing or preventing toxicity of chemical or biological substances is important, the agency also asked when, if ever, it is ethical to expose volunteers to toxic chemical and biological substances to test the efficacy of products that may be used to provide potential protection against those substances.

Third, because these products are critically important, even if they cannot be ethically tested in humans to demonstrate efficacy, the agency asked what evidence of efficacy, other than that from human trials, would be appropriate to demonstrate the safety and efficacy of products that may provide protection against toxic chemical and biological substances.

In a related document published elsewhere in this issue of the **Federal Register**, FDA has addressed the second and third issues in a proposed regulation that discusses the evidence needed to demonstrate efficacy of new drugs for use against lethal or permanently disabling toxic substances when definitive efficacy studies in humans cannot ethically be conducted. The agency believes that, if issued, this proposed rule may make it possible to develop evidence sufficient to support approval of such drugs and thus should help minimize the need to use investigational products in military exigencies.

With respect to the first question, waiver of informed consent in military operations, FDA's decision to revoke the 1990 interim rule is based on consideration of all relevant facts, including FDA's evaluation of DOD's experience during the Persian Gulf War, FDA's analysis of the comments received in response to the first issue addressed in the July 1997 request for comments on whether the agency should revise or revoke the interim rule (62 FR 40996), and the recent enactment of the Defense Authorization Act.

Section 731 of the Defense Authorization Act, amending 10 U.S.C.

1107(f), became effective on October 17, 1998. Under 10 U.S.C. 1107(f), the Commissioner of Food and Drugs no longer has the authority to make waiver of informed consent decisions in military operations because 10 U.S.C. 1107(f)(1) explicitly vests the authority to waive the act's informed consent requirement in the President. Section 1107(f)(1) of Title 10 provides for such waiver in the case of the administration of an investigational new drug or drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation. Section 1107(f)(1) of Title 10 authorizes the President to waive informed consent if the President finds that obtaining informed consent is: (1) Not feasible; (2) contrary to the best interests of the member; or (3) not in the interests of national security. The first two grounds (lack of feasibility or contrary to the best interests of recipients) are specified in section 505(i) of the act (21 U.S.C. 355(i)).

Section 1107(f)(2) of Title 10 provides that, in making a determination to waive informed consent on the grounds that it is not feasible or contrary to the best interests of the armed services member, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior consent requirement on that ground.

Because section 1107(f)(1) of Title 10 refers to waiver of informed consent in connection with military operations, the relevant FDA regulations referenced in section 1107(f)(2) of Title 10 would be any regulations dealing with waivers in this context. As discussed previously, FDA originally issued such regulations as an interim final rule in 1990 (55 FR 52814, December 21, 1990), at § 50.23(d)(1) through (d)(4). These regulations consisted of procedures to be followed by the Assistant Secretary of Defense (Health Affairs) and the Commissioner of Food and Drugs (§ 50.23(d)(1)); standards and criteria for granting such waivers (§ 50.23(d)(1) and (d)(2)); a discretionary provision for consultation with advisory committees (§ 50.23(d)(3)) and time limits for such waivers (§ 50.23(d)(4)). These regulations conflict with section 1107(f)(1) of Title 10 in that they vest FDA's Commissioner with the authority to make such waiver decisions.

As reflected in a number of the comments FDA received on the 1990 interim rule, many people addressed the issue of whether waiver of informed consent in military operations involving military personnel is ever acceptable, and if so, when. In the Defense Authorization Act, Congress has addressed that issue by explicitly providing for waiver of the informed consent requirement by the President in certain situations. In light of the immediate effective date of the Defense Authorization Act, the agency believes that it is critical to have in place adequate criteria and standards for the President to apply in making an informed consent waiver determination.

Based on the extensive examination of issues associated with the existing interim final rule during the last 8 years, the agency has developed a new rule consistent with the Defense Authorization Act that contains new strengthened criteria and standards that the President can use in making informed consent waiver determinations. The agency believes that it is in the public interest to have these new criteria and standards in place and available for use should the President be called upon to make a waiver determination while, at the same time, it solicits public comments on these criteria and standards. These new criteria and standards are discussed in greater detail later in this document.

II. Comments Received on Whether to Revoke or Amend the 1990 Interim Rule

The agency received 134 comments on whether it should revoke or amend the 1990 interim rule: Of these, 119 comments expressed opposition to the interim rule and recommended that it be permanently revoked, 7 comments recommended changes to the interim rule, 2 comments supported retention of the interim rule, and 6 comments misunderstood the scope of the interim rule and provided comments on a different regulation.

A. Summary of Comments Recommending That the Interim Rule Be Revoked

The 119 comments that recommended the revocation of the interim rule were signed by 160 individuals including veterans, veterans' relatives, active military personnel, active military families, ethicists, physicians, other health care providers, and private citizens, as well as from an advocacy group for ailing Persian Gulf Veterans, an organization representing grassroots veterans' organizations in America and England, and a nonprofit public interest organization.

Most of these comments opposed the agency's continued use of the interim rule after the experience of the Persian Gulf War. Many thought it should never have been used. Specifically, 114 comments stated that informed consent was absolutely essential and that military personnel, like other nonmilitary citizens, should receive adequate information about an investigational product before its use and have the right to refuse to receive it. Seventeen comments stressed the need for followup of possible adverse reactions to investigational products, and 15 comments indicated that DOD could not fulfill its responsibilities even if FDA required adequate followup and other requirements as part of a new regulation. Five comments stated that DOD had shown itself to be incapable of adequate oversight and recordkeeping and three comments noted that the interim rule had not been implemented by DOD as had been intended. Several comments suggested that if the rule were to be used again, there must be an independent board of medical and ethical experts, there must be an institutional review board independent of DOD, and there must be proper monitoring that could only be done by non-DOD personnel.

As described earlier in this document, The Defense Authorization Act answers the controversial question of whether waiver of informed consent in military operations is ever appropriate. In passing this legislation, Congress has concluded that the President may waive the informed consent requirement for military personnel engaged in a particular military operation in certain situations. The comments on the 1990 interim rule pointed out significant areas that needed to be strengthened, including: Provision of adequate information about an investigational product before its use; adequate followup to assess whether there are adverse health consequences that result from the use of the investigational product; adequate oversight, accountability, and recordkeeping when investigational agents are used; and involvement of non-DOD personnel in decisions to use investigational products without informed consent. All of these areas have been addressed in the new interim rule that establishes the criteria and standards for the President to use in making an informed consent waiver determination.

B. Summary of Comments Recommending Changes to the Interim Rule

Seven comments recommended changes to the interim rule. Three of these comments recommended that the rule be suspended and reconsidered only if their modifications were adopted and adhered to by DOD.

Two comments recommended that a process be established for the President

to authorize the use of investigational products without informed consent in military conflicts.

The Defense Authorization Act establishes the President as the sole authority for making a waiver of informed consent determination for military personnel involved in a particular military operation. Thus, the process recommended by these comments has already been established through legislation. FDA will be involved in this process through its traditional role of reviewing specific protocols under its investigational new drug (IND) regulations.

One comment recommended that the rule be amended to require: (1) That reasonable efforts be made to inform individuals in advance that investigational products are to be used, (2) that the extent and appropriateness of the information provided be determined by the Commissioner of FDA, (3) that all individuals exposed to investigational products be informed no later than 1 year after their use, and (4) that there be established a publicly accessible site for continuous access to the most updated scientific information on these products.

The agency agrees with this comment and has incorporated the suggested requirements into the new interim rule. The interim rule requires that each member involved in the military operation be given, prior to the administration of the investigational new drug, a specific written information sheet. That information sheet is to include information (in addition to information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product. Under 10 U.S.C. 1107(d), the information sheet is required to contain the following: (1) Clear notice that the drug being administered is an investigational new drug or a drug unapproved for its applied use; (2) the reasons why the investigational new drug or drug unapproved for its applied use is being administered; (3) information regarding the possible side effects of the investigational new drug or drug unapproved for its applied use, including any known side effects possible as a result of the interaction of such drug with other drugs or treatments being administered to the members receiving such drug; and (4) such other information that, as a condition of authorizing the use of the investigational new drug or drug unapproved for its applied use, the Secretary of Health and Human Services may require to be disclosed. FDA intends to review the information sheet as part of its review of the use of the investigational product under an IND in order to determine its adequacy. The interim rule also requires DOD to provide public notice in the **Federal Register** describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, as well as other pertinent information.

One comment from an individual who was employed at the U.S. Army Medical Materiel Development Activity, Ft. Detrick, MD, during the Gulf War, and who served for 22 years as an Army officer, stated that "[a]s the largest training organization in the United States, perhaps in the world, DoD clearly has the capacity and resources to provide adequate information to each service member before he or she takes or uses an investigational product." Based on this reasoning, the Army officer suggested that the rule be amended and that DOD could, and should, institute training programs early in each service member's military career. Specifically, this comment recommended that FDA demand adequate training as part of the informed consent process and require that DOD develop and validate training guidelines for the use of investigational products that might be used under a waiver during all phases of product development.

The agency agrees with this comment. The interim rule now requires DOD to provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

Two comments stressed that FDA should regard itself as acting on behalf of the troops, not on behalf of the military or the DOD. These comments recommended that the interim rule be suspended or revoked until the agency critically reviewed requests from DOD to waive informed consent that contained the following documentation: (1) Documentation from DOD that identified the threat, its nature, and its likelihood; (2) documentation from DOD that administration of the proposed treatment is likely to be effective against that threat; (3) documentation from DOD that detailed concurrent conditions (such as environmental and occupational conditions, treatment regimens that may be employed by troops serving in the forces to be treated) that could alter the effects of the proposed treatment; (4) documentation from DOD that demonstrated that military medical services are capable of delivering qualified personnel and adequate supplies of necessary medical material to the specific theater of operations; (5) documentation from DOD that establishes that the recordkeeping systems are capable of tracking the proposed treatment from supplier to point of administration; and (6) documentation that demonstrates that there are medical followup plans for troops receiving the proposed treatment. These comments stated that this documentation should be made public and public comment should be sought regarding the performance of both DOD and FDA. These comments stated that if these requirements could be met, adequate information would need to be provided to the troops by individuals with whom they have daily contact.

The agency agrees with the suggestions for documentation contained in these comments and has incorporated them into the new interim rule. Under the new interim rule, each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet. This information sheet is required, under 10 U.S.C. 1107(d), to contain specific information. The interim rule incorporates this requirement by reference and requires the disclosure of risks and benefits of the use of the investigational product, potential side effects, and other pertinent information about the appropriate use of the product.

C. Comments in Support of Retaining the Interim Rule

The agency received two comments in support of retaining the interim rule as written—one from DOD and the other from a physician from academia. This latter comment stated that:

> [t]he organization and activities of the DOD are not meant to be either democratic or reliant upon informed consent. However, the goal of DOD activities in combat situations is victory, and with that end in sight, it is reasonable to expect that the condition of the troops is considered carefully by DOD leadership. Decisions pertinent to the use of investigational drugs without informed consent will most likely represent the best interests of military personnel and the nation.

DOD's comments in support of maintaining the interim rule were similar to those expressed by DOD in requesting the interim rule initially (see the Assistant Secretary of Defense (Health Affairs) letter of October 30, 1990, to the Assistant Secretary for Health, HHS, quoted in the preamble to the interim rule (55 FR 52814), and in its September 13, 1996, response to the

May 7, 1996, petition to FDA requesting that the Commissioner repeal the interim rule (see summary in the July 1997 request for comments (62 FR 40996 at 41000)).

As previously stated, Congress now has passed legislation providing for waiver of the informed consent requirement by the President in certain military situations, thus, recognizing the need for waiver in limited situations. The agency, however, believes that the criteria and standards contained in the 1990 interim rule are not sufficient and has therefore established new criteria and standards for the President to apply in making an informed consent waiver determination.

D. Other Comments on the Interim Rule

A comment from Chairman Arlen Specter and Ranking Minority Member John D. Rockefeller IV, Senate Committee on Veterans' Affairs, stated that whether the rule should be revoked or not "* * * is a complex decision that needs to be carefully considered, with input from health care professionals, ethicists, active duty military personnel, veterans, and the general public." They urged FDA, if it decided not to revoke the rule, to ensure that a process is instituted to provide maximum protection to "* * * the health and well-being of military personnel prior to, during, and subsequent to a combat situation." They stressed the importance of establishing a process prior to any combat situation that would: (1) Lay out how decisions would be reached in a timely manner; (2) require institutional review boards (IRB's) used during this process to consist of at least three persons independent of DOD because the IRB will be making decisions that result in the loss of rights of a large group of individuals and objectivity is essential; (3) require health surveillance data from well-designed data collection forms be used to assess the potential health consequences of the use of products and to modify decisions as information is gained; and (4) require compliance with mechanisms for review and sanctions be put in place.

The agency agrees that the decisions associated with the interim rule have been complex and there is a need to institute a process that will provide maximum protection to military personnel. The Defense Authorization Act vests authority in the President to make a waiver of informed consent determination, and it vests in the President the process by which such decisions shall be made. FDA believes that this process, which includes use of the criteria and standards in the new interim final rule, will provide the protection of the health and well-being of military personnel urged by the comments. As suggested by this comment, the new interim rule requires the IRB to include at least three nonaffiliated members who are not employees or officers of the Federal Government.

In response to the suggestion that the rule require health surveillance to assess the potential health consequences of the use of the product and to modify decisions as information is gained, the new interim rule contains two provisions. One requires DOD to provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product. The second requires DOD to report to FDA and to the President any changed circumstances relating to the standards and criteria contained in the rule or that otherwise might affect the determination to use an investigational new drug without informed consent.

In response to the comment's recommendation that the process require compliance with mechanisms for review and sanctions, the agency notes that the Defense Authorization Act requires the Secretary of Defense, if the President grants the requested waiver, to submit to the chairman and ranking minority member of each congressional defense committee a notification of the waiver, together with the written determination of the President and the Secretary of Defense's justification for the request for the waiver of informed consent (see 10 U.S.C. 1107(f)(3)(B)). The new interim rule builds in accountability and compliance by requiring the Secretary of Defense to certify and document to the President that the standards and criteria in the rule have been met, including the criteria that use of the investigational drug without informed consent otherwise conforms with applicable law. Further, the new interim rule notes that "[n]othing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations." The agency notes that the mechanisms for review and sanctions under the IND regulations apply to the DOD and its employees involved in the use of products subject to FDA regulation.

In response to the comment's suggestion that the process include public disclosure, the new interim rule requires DOD to provide public notice in the **Federal Register** as soon as practicable and consistent with classification requirements describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

The agency has concluded that the issues associated with the 1990 interim rule are very complex and difficult, as recognized by Senators Specter and Rockefeller. As described in detail in FDA's July 1997 request for comments, there has been extensive examination of issues associated with the 1990 interim rule during the last 8 years. In addition to FDA's July 1997 request for comments, the issues have been examined in comments submitted to the agency in the 30-day comment period following the rule's publication in the **Federal Register** on December 21, 1990; in litigation (*Doe* v. *Sullivan*, 756 F. Supp. 12, 14 (D.D.C. 1991)); in a May 6, 1994, United States Senate Committee on Veterans' Affairs hearing on "Is Military Research Hazardous to Veterans' Health? Lessons From World War II, the Persian Gulf, and Today;" reviews conducted by the Presidential Advisory Committee on Gulf War Veterans' Illnesses; and in the Public Citizen, the National Veterans Legal Services Program, and the National Gulf War Resource Center, Inc., May 7, 1996, petition to FDA requesting that the Commissioner repeal the interim rule.

The agency believes that exceptions from the informed consent requirement should apply rarely and only when sufficient additional protections are provided to the military personnel affected.

III. Revocation of the 1990 Interim Rule

The agency recognizes that there may be future military combat situations where U.S. military personnel are at risk of exposure to chemical and biological weapons and that DOD has a critical and legitimate interest in protecting military personnel from such chemical and biological agents. This was the basis for FDA's 1990 interim rule issued in anticipation of the Persian Gulf War that gave DOD the authority to use specified investigational products to provide potential protection against chemical and biological warfare agents without obtaining informed consent from individual service personnel.

A. DOD's Experience in Implementing the Rule During the Persian Gulf War

DOD's experience during the Gulf War with pyridostigmine bromide and the botulinum toxoid vaccine was described in detail in the July 1997 request for comments (62 FR 40996 at 40998 through 41000). A brief summary of this experience follows.

In December 1990, DOD submitted protocols under IND's and requests for waiver of informed consent for: (1) Pyridostigmine bromide 30-milligram tablets, a potentially useful pretreatment against soman, a nerve gas; and (2) the botulinum toxoid vaccine, potentially protective against toxins produced by *Clostridium botulinum* (the bacterium that produces the toxin that causes botulism). The Commissioner approved both of DOD's waiver requests and each product was administered to some of the military personnel who participated in Operation Desert Storm. FDA's agreement to waive the informed consent requirement was based, in large part, on DOD's agreement to provide and disseminate specified information on these products to military personnel and upon adherence to labeling and other prescribed requirements for the use of investigational products.

Concurrent with the agency's request for comments on the interim rule, FDA was also evaluating DOD's experience in implementing IND's, as well as waivers under the interim rule, during the Gulf War in order to obtain specific factual information and to assess DOD's compliance with FDA requirements. In the agency's ongoing evaluation of the use of investigational products in the Persian Gulf, the agency identified significant deviations from Federal regulations published in Title 21, Code of Federal Regulations (CFR), parts 50 and 312 (21 CFR parts 50 and 312). These deviations were set forth in a July 22, 1997, and a December 2, 1997, letter from the Lead Deputy Commissioner of the Food and Drug Administration to the Acting Deputy Secretary of Defense for Health Affairs (Refs. 1 through 3). The noted deviations, and the relevant observations that formed the basis for the conclusion that deviations had occurred, are summarized in the following paragraphs.

1. Pyridostigmine Bromide

There was a failure to meet the conditions set by the Commissioner for granting a waiver from the informed consent requirements under the 1990 interim rule for pyridostigmine bromide. FDA's agreement to waive the informed consent requirement at the time of the Gulf War was based, in large part, on DOD's agreement to provide and disseminate information on pyridostigmine to all military personnel. Based on DOD statements to FDA as well as FDA's own evaluation, FDA has concluded that the information sheet on pyridostigmine was not provided and disseminated to military personnel in the Gulf as required by the Commissioner's letter granting the waiver under the interim rule. Because inadequate information was provided to the soldiers, at least some soldiers either took the wrong amount of pyridostigmine or disregarded orders to take it completely.

There was a failure to collect, review, and make reports of adverse experiences attributed to the use of pyridostigmine bromide in a timely manner. Although the agency waived the requirements of § 312.32 in regard to the 3- and 10-day time limits for the reporting of adverse experiences, the agency expected DOD to make a reasonable effort to collect, review, and make reports of adverse clinical consequences attributed to the use of the product in as timely a manner as conditions permitted.

There was a failure to label pyridostigmine bromide with investigational labeling as required by FDA regulations. FDA had agreed, as requested by DOD, to waive the provisions of § 312.6 in order to allow DOD to employ the phrase "For military use and evaluation" in place of the statement ordinarily mandated for use on the immediate package of an investigational drug product, which reads "Caution: New Drug—Limited by Federal (or United States) Law to Investigational Use". FDA's waiver of the standard statement was on condition that all of the product distributed to service members would carry the new "military use" labeling. Based on information provided to the agency, FDA believes that the pyridostigmine bromide distributed to military personnel in the Persian Gulf was not labeled as required by the conditions of the waiver.

2. Botulinum Toxoid Vaccine

There was a failure to ensure that the investigation was conducted in accordance with the general investigational plan for the botulinum toxoid vaccine during the Gulf War. The protocol for the botulinum toxoid vaccine stated that each botulinum toxoid vaccine dose was to be recorded in the individual's permanent immunization record. This was not done.

There was also a failure to maintain adequate records showing the receipt, shipment, and disposition of the investigational product botulinum toxoid vaccine as required by §§ 312.57 and 312.59.

On January 8, 1991, FDA granted DOD's request for a waiver of informed consent under the interim final rule for use of the botulinum toxoid vaccine during the Gulf War. However, following the cessation of combat activities DOD advised FDA in a March 15, 1991, letter that the military command in the theater of operations in the Persian Gulf decided to administer the botulinum toxoid vaccine on "a voluntary basis." This letter did not state whether informed consent was obtained.

The military command's decision to allow administration of the vaccine on a voluntary basis indicates that the criteria for granting a waiver under the interim rule was no longer met; specifically that "* * * preservation of the health of the individual and the safety of other personnel require that a particular treatment [botulinum toxoid vaccine] be provided to a specified group of military personnel, without regard to what might be an individual's personal preference for no treatment or for some alternative treatment." If the criteria for waiver were not met, DOD was required to obtain and document the informed consent of military personnel receiving the vaccine in accordance with §§ 50.25 and 50.27. Without signed consent forms to document that informed consent was obtained, and based on testimony from Persian Gulf War veterans that information on the vaccine was not uniformly given to military personnel, the agency has concluded that informed consent was not routinely obtained from military personnel who received the botulinum toxoid vaccine in accordance with FDA regulations.

Experience with the use of the waiver provision of the 1990 interim rule suggests two conclusions: (1) To the extent possible, military personnel should receive treatments whose safety and effectiveness have been fully evaluated; (2) where it is necessary to utilize investigational agents and to waive informed consent, new standards and criteria for doing so should be developed that will better ensure protection of the troops receiving the investigational product.

B. Future Use of FDA-Regulated Products by DOD

FDA has concluded that there are important ways for the agency to contribute to DOD's mandate to protect military personnel that are consistent with FDA's mission and regulations. FDA's existing mechanisms for providing access to investigational products under an IND will continue to be available to any entity that complies with the agency's specified requirements. Both DOD and FDA recognize, however, that some of the IND requirements may not be feasible in certain combat situations. Based on the lessons from use of investigational agents during the Gulf War, the agency

believes that DOD's needs can best be met through DOD's support of drug development efforts leading to approval of products found to be safe and effective.

FDA shares DOD's goal of getting the best products to military personnel. Thus, FDA is committed to working with DOD to resolve the safety and effectiveness questions that may allow FDA to approve the drug and biological products for use in military operations and during military exigencies. In order to provide pharmaceutical agents that are safe and effective in protecting military personnel, the agency believes that DOD must focus its efforts on drug development. The agency notes that under existing regulations it can expedite access to new drugs by accelerating approval (subpart H of 21 CFR part 314 and subpart E of 21 CFR part 601). In addition, consistent with the recent changes to the act on fast track products made in the Food and Drug Administration Modernization Act of 1997, FDA is committed to facilitating development and expediting the review of drugs for serious and life-threatening conditions that address unmet needs (section 506 of the act (21 U.S.C. 356)). Moreover, FDA is proposing an additional mechanism for product approval that is described elsewhere in this issue of the **Federal Register** and that relates to the evidence needed to demonstrate safety and efficacy for drug and biological products for use against lethal or toxic substances when efficacy studies in humans cannot ethically be conducted.

In order to minimize the need to use investigational products during military exigencies, DOD and FDA have formed a working group for the purpose of assisting DOD in its drug development efforts related to these products. DOD has agreed to identify those products that may provide protection to military members, develop appropriate drug development plans for each product, and establish a timeframe for completion.

FDA recognizes, however, that in rare instances investigational products may need to be used by DOD in deployment situations. The enactment of the Defense Authorization Act reflects this fact and calls for the implementation of a process that will help ensure that when informed consent is waived it will be done under standards and criteria that will help protect the troops receiving the investigational product. Accordingly, FDA has issued this new interim rule.

IV. Establishment of New Standards and Criteria

A. Description of New Interim Rule

As described earlier, under 10 U.S.C. 1107(f), the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent and that the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible, is contrary to the best interests of the military member, or is not in the interests of national security. The statute further provides that in making this determination based on the grounds that it is infeasible or contrary to the best interests of the military member, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements. This interim rule contains those standards and criteria. The statute is silent about the standards and criteria that the President is to apply in making a determination that obtaining consent is not in the interests of national security.

The Defense Authorization Act authorizes the Secretary of Defense to request an informed consent waiver determination from the President. The interim rule requires the Secretary of Defense to certify and document to the President that the standards and criteria in the interim rule have been met.

Section 50.23(d)(1)(i) through (d)(1)(iv) contain the fundamental information necessary to make an informed assessment of risks and benefits. Under these paragraphs, the Secretary of Defense must certify and document that: (1) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND; (2) the military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness; (3) there is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug; and (4) conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and threaten the accomplishment of the military mission.

The requirements for IRB review of protocols for military use of investigational drugs without informed consent have been strengthened and further specified. Following the Gulf War, the agency became aware that a military IRB, upon initial review of the proposed use of the botulinum toxoid vaccine in anticipation of the Gulf War, had recommended that the vaccine be provided with informed consent (Ref. 4). The proposed use was subsequently reviewed by a different military IRB that approved its use without informed consent. It is not clear whether the conclusions of the initial IRB were shared with the subsequent IRB. In order to ensure adequate and meaningful IRB review, § 50.23(d)(1)(v) requires the duly constituted IRB to be responsible for the review of the study and requires that the IRB review and approve the investigational new drug protocol and the administration of the investigational new drug without informed consent as a prerequisite for the study to proceed. It also requires DOD's request for a waiver to include the documentation of minutes of IRB meetings at which the protocol was reviewed. This documentation of minutes is required by 21 CFR 56.115(a)(2).

Section 50.23(d)(2) describes additional requirements that pertain to this IRB that are not contained in FDA's IRB regulations part 56 (21 CFR part 56). The IRB must include at least 3 nonaffiliated members who are not employees or officers of the Federal Government (other than for purposes of membership on the IRB). The quorum required for a convened meeting must include a majority of the members including at least one member whose primary concerns are in nonscientific areas, and, if feasible, a majority of the nonaffiliated members. The minutes of IRB meetings at which the protocol is reviewed are to be provided to the Secretary of Defense for further review.

Section 50.23(d)(3) describes additional review requirements that pertain to this IRB. For the study to be able to proceed, the IRB must review and approve the contents of the required written information sheet on the investigational product; the adequacy of the plan to disseminate information, including the information sheet and other information (e.g., in forms other than written), to potential recipients; the adequacy of the information and the plans for its dissemination to health care providers, including potential side

effects, contraindications, potential interactions, and other pertinent considerations; and an informed consent form, as required by part 50, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved. In addition, § 50.23(d)(4) requires DOD to submit to FDA summaries of IRB meetings at which the proposed protocol has been reviewed.

In order to help ensure that the President is provided all relevant information related to the effects of the investigational drug, § 50.23(d)(1)(vi) requires the Secretary of Defense to certify and document in his or her request for a waiver determination under § 50.23(d)(1) that DOD has explained: (1) The context in which the investigational drug will be administered; (2) the nature of the disease or condition for which the preventive or therapeutic treatment is intended; and (3) to the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

In order to help ensure better recordkeeping than occurred during the Gulf War, § 50.23(d)(1)(vii), (d)(1)(ix), and (d)(1)(x) require the Secretary of Defense to document and certify that DOD's recordkeeping system is capable of tracking, and will be used to track the proposed treatment from the supplier to the individual recipient; that medical records of members involved in the military operation will accurately document the receipt by members of the notification required by § 50.23(d)(1)(viii) as well as any investigational new drugs in accordance with FDA regulations.

In order to help ensure that each military member is provided adequate information on the investigational product, § 50.23(d)(1)(viii) requires the Secretary of Defense to document and certify that each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet containing specified information. Section 50.23(d)(1)(xiv) requires the Secretary of Defense to document and certify that DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

In response to comments that DOD must provide adequate followup to determine whether there are adverse consequences to the use of investigational products, § 50.23(d)(1)(xi) requires the Secretary of Defense to document and certify that DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

Because the agency believes that exceptions to the informed consent requirement should be made rarely and in narrow circumstances and that it is preferable to establish the safety and efficacy of products before their general use in large populations, § 50.23(d)(1)(xii) requires the Secretary of Defense to certify and document that DOD is pursuing drug development for the investigational drug (that could be used in a deployment situation), including a time line for such development, and marketing approval with due diligence. The rule contains two provisions to help ensure that informed consent waiver determinations continue to meet the standards and criteria of this rule after an initial waiver has been granted by the President. Section 50.23(d)(1)(xv) requires the Secretary of Defense to certify and document that DOD has stated and justified the time period for which the waiver is needed, not to exceed 1 year. For a waiver to exceed 1 year, this paragraph requires such a waiver to be separately renewed under the standards and criteria contained in § 50.23(d). Section 50.23(d)(1)(xvi) places a continuing obligation on DOD to report to the FDA and to the President any changed circumstances relating to these standards and criteria or that otherwise might affect the determination to use an investigational new drug without informed consent.

Section 50.23(d)(1)(xiii) has been included in order to ensure that FDA has completed its review of the investigational new drug protocol and concluded that it may proceed subject to a decision by the President on the informed consent waiver request. FDA will provide a written notification to DOD after it has completed its review of the investigational new drug protocol. This notification may either grant permission for the protocol to proceed subject to the President's decision on the informed consent waiver request or it may place the study on clinical hold. DOD should not proceed with a protocol under this rule until it has received notification from FDA that the protocol may proceed. As discussed later in this document, the agency has adopted a change in part 312 to help ensure that the IND review process is efficiently applied to the use of investigational products under this rule.

In response to a number of comments, discussed previously, that encouraged public access to information about products for which an informed consent waiver is granted, the agency has included § 50.23(d)(1)(xvii) in the rule. This paragraph requires DOD to provide public notice as soon as practicable and consistent with classification requirements through notice in the **Federal Register** describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

Finally, in order to help ensure that DOD adheres to applicable statutes and laws, § 50.23(d)(1)(xviii) requires the Secretary of Defense to document and certify that the use of the investigational drug without informed consent otherwise conforms with applicable law. Section 50.23(d)(5) states that "[n]othing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations."

B. Description of Conforming Amendments

This interim rule necessitates a change to the regulations for human drugs so that those regulations are consistent with this rule. The agency is amending § 312.42 to explicitly state that an investigation may be placed on clinical hold pending a determination by the President to waive the prior consent requirement for the administration of an investigational new drug. If the agency invokes this reason for a clinical hold, it will mean that the agency has completed its review of the protocol and has concluded that the study may proceed; however, subjects may not be enrolled in the study until a positive decision on the informed consent waiver request has been made by the President and FDA has provided written notification to DOD that the clinical hold has been removed.

V. Request for Comments

Interested persons may, on or before December 20, 1999, submit to the Dockets Management Branch (address above) written comments regarding this rule. 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.

FDA is revoking the December 21, 1990, interim rule and issuing a new interim rule in its place effective on date of publication in the **Federal Register**. FDA is proceeding without notice and comment rulemaking because of the

significant need to have regulations in place that are consistent with recently enacted legislation addressing waiver of informed consent in military operations and that provide adequate standards and criteria for such waiver determinations. As described in more detail in the following paragraphs, FDA finds, in accordance with section 553(b) of the Administrative Procedure Act, that it would be impracticable and contrary to the public interest to provide for notice and comment prior to the revocation of the December 1990 rule and the issuance of the new interim rule.

The statutory provision in the Defense Authorization Act that vests authority for waiver decisions in the President overrides the 1990 rule vesting authority for such waiver decisions in the Commissioner. Thus, it invalidates those parts of the 1990 regulation that are inconsistent with the Defense Authorization Act. The new interim rule corrects this inconsistency by acknowledging the existence of the Defense Authorization Act and its grant of waiver authority to the President. To require notice and comment to make this correction is unnecessary in that the new rule codifies in regulation a clear statutory mandate.

Since the issuance of the 1990 interim rule, there has been extensive public discussion regarding the rule on numerous occasions (see discussion in section II of this document). After considering all the relevant facts, including the comments received on the July 1997 request for comments, and FDA's evaluation of DOD's experience during the Persian Gulf War in implementing the 1990 rule, FDA has concluded that the rule did not work as intended. In light of the enactment of the Defense Authorization Act, with an immediate effective date and because the President could be called upon to make a waiver determination for military personnel engaged in a specific military operation at any time, the agency believes that it is critical to have in place adequate criteria and standards for the President to apply in making an informed consent waiver determination. Modifying the 1990 rule to conform to the statute, without adding the additional protections provided in this new rule is contrary to the public interest because it would leave in place, during the comment period, procedures now considered insufficient. As discussed previously, FDA has developed new strengthened criteria and standards that the President can use in making informed consent waiver determinations. Accordingly, the agency believes it is in the public interest to have these new criteria and standards in place while, at the same time, it solicits public comment.

It is, therefore, in the public interest, to establish quickly, through this new interim final rule, stringent criteria and standards for the President's application. Following the comment period, the agency intends promptly to publish a final rule.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

VII. Executive Order 12612: Federalism

Executive Order 12612 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant effect on federalism. Using the criteria and principles set forth in the order, FDA has considered the impact of the interim rule on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of Government. FDA concludes that this rule is consistent with the principles set forth in Executive Order 12612.

Executive Order 12612 states that agencies formulating and implementing policies are to be guided by certain federalism principles. Section 2 of Executive Order 12612 enumerates fundamental federalism principles. Section 3 of Executive Order 12612 states that, in addition to these fundamental principles, executive departments and agencies shall adhere, to the extent permitted by law, to certain listed criteria when formulating and implementing policies that have federalism implications. Section 4 of Executive Order 12612 lists special requirements for preemption.

Section 4 of Executive Order 12612 states that an executive department or agency foreseeing the possibility of a conflict between State law and federally protected interests within its area of regulatory responsibility is to consult with States in an effort to avoid such conflict. Section 4 of Executive Order 12612 also states that an executive department or agency proposing to act through rulemaking to preempt State law is to provide all affected States notice and opportunity for appropriate participation in the proceedings. As required by the Executive Order in section 4(d) and (e), States have, through this notice of proposed rulemaking, an opportunity to raise the possibility of conflicts and to participate in the proceedings. Consistent with Executive Order 12612, FDA requests information and comments from interested parties, including but not limited to State and local authorities, on these issues of federalism.

VIII. Analysis of Impacts

FDA has examined the impacts of the rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). If a rule would have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize these impacts. Title II of the Unfunded Mandates Reform Act (Public Law 104–4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation).

The agency believes that the revised rule is consistent with the regulatory philosophy and principles identified in the Executive Order and in these two statutes. The agency has determined that this rule is a "significant regulatory action" as defined in section 3(f)(4) of Executive Order 12866 because it raises novel policy issues. To the extent that any of the standards and criteria entail costs to the DOD, these standards and obligations are already assumed by DOD; they are enunciated here to stress their importance to safeguarding the health and welfare of military personnel to minimize the need to use this rule. With respect to the Regulatory Flexibility Act (5 U.S.C. 605(b)), any economic cost of the rule would be incurred only by DOD, which is not a small entity. Therefore, the agency certifies that the rule will not have significant economic impact on a substantial number of small entities. Under the Regulatory Flexibility Act, therefore, no further analysis is required. Similarly, because the rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in a 1-year expenditure of $100 million or more,

FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act.

IX. Paperwork

This interim final rule contains no collections of information subject to the Paperwork Reduction Act of 1995.

X. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Letter from the Lead Deputy Commissioner, FDA, to the Acting Deputy Secretary of Defense for Health Affairs, July 22, 1997.

2. Letter from the Army Surgeon General to the Lead Deputy Commissioner, FDA, responding to the July 22, 1997, letter, October 23, 1997.

3. Letter from the Lead Deputy Commissioner, FDA, to the Acting Deputy Secretary of Defense for Health Affairs, December 22, 1997.

4. Memorandum for record, minutes of the October 4, 1990, ninety-third meeting of the U.S. Army Medical Research Institute of Infectious Diseases Human Use Committee, October 5, 1990.

List of Subjects

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 50 and 312 are amended as follows:

PART 50—PROTECTION OF HUMAN SUBJECTS

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

Authority: 21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b–263n.

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

§ 50.23 Exception from general requirements.

* * * * *

(d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to 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) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by § 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

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

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific

investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the **Federal Register** describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by § 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

4. Section 312.42 is amended by adding paragraph (b)(6) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(6) Clinical hold of any investigation involving an exception from informed consent under § 50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under § 50.23(d) of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

* * * * *

Dated: May 25, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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