Department of Defense

# DIRECTIVE

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ASD(HA)

SUBJECT: Use of Investigational New Drugs for Force Health Protection

References: (a) Section 1107 of title 10, United States Code
(b) Executive Order 13139, "Improving Health Protection of Military Personnel Participating in Particular Military Operations," September 30, 1999
(c) Title 21, Code of Federal Regulations, Parts 50, 56, 312, Subpart I of Part 314, Subpart G of Part 601, current edition
(d) House Report No. 105-736, Conference Report to Accompany Proposed Strom Thurmond National Defense Authorization Act for Fiscal Year 1999, page 685
(e) through (f), see enclosure 1

## 1. PURPOSE

This Directive:

1.1. Establishes policy and assigns responsibility for compliance with references (a) through (c) for the use of investigational new drugs for force health protection.

1.2. Designates the Secretary of the Army as the DoD Executive Agent for the use of investigational new drugs for force health protection.

## 2. APPLICABILITY AND SCOPE

This Directive:

2.1. Applies to the Office of the Secretary of Defense, the Military Departments, the Chairman of the Joint Chiefs of Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities and all other organizational entities within the Department of Defense (hereafter referred to collectively as "the DoD Components").

2.2. Applies to all uses of investigational new drugs by the Department of Defense for force health protection.

2.3. Does not apply to actions by DoD healthcare providers that are within standard medical practice in the United States and are not subject to FDA regulations at reference (c).

## 3. DEFINITIONS

3.1. Force Health Protection. An organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions.

3.2. Investigational New Drug (IND). A drug or biological product subject to the FDA regulations at 21 CFR Part 312 (reference (c)), including:

3.2.1. A drug not approved or a biological product not licensed by the FDA.

3.2.2. A drug unapproved for its applied use.

3.3. Drug Unapproved for Its Applied Use. A drug or biological product administered for a use not described in the labeling of the drug or biological product approved by the FDA (referred to in subsection (g)(2) of reference (a)), and for which FDA requirements of use authorization and prior informed consent (referred to in subsections (d)(4) and (f)(1) of reference (a)) are applicable, but not including uses to which those requirements are inapplicable based on standard medical practice in the United States (referred to in reference (d)).

3.4. Particular Military Operations. A military operation or specific military mission or function, which involves any chemical, biological, or radiological warfare or endemic disease threats.

4. POLICY

It is DoD policy that:

4.1. Force Health Protection. Personnel carrying out military operations shall be provided the best possible force health protection, including safe and effective medical countermeasures to chemical, biological or radiological warfare and endemic disease threats.

4.1.1. The DoD Components shall make preferential use of products approved by the FDA for general commercial marketing, when available, to provide the needed medical countermeasure.

4.1.2. When no FDA-approved product is available to meet a foreseeable threat, the Secretary of the Army, as Executive Agent, shall carry out appropriate research and development program activities directed toward obtaining general commercial marketing approval by the FDA of safe and effective medical countermeasures. Such activities shall include use of special FDA rules at 21 CFR subpart I of part 312 and subpart G of part 601 (reference (c)) for the approval of new drugs and biological products for use against lethal or permanently disabling toxic substances when efficacy studies in humans cannot be conducted ethically.

4.1.3. When, at the time of the need for a force health protection countermeasure against a particular threat, no safe and effective FDA-approved drug or biological product is available, the DoD Components may request approval of the Secretary of Defense to use an IND. Such requests must be justified based on the available evidence of the safety and efficacy of the drug and the nature and degree of the threat to personnel.

4.1.4. When using INDs for force health protection, the DoD Components shall comply with 10 U.S.C. 1107, E.O. 13139, and applicable FDA regulations (references (a) through (c)).

4.2. Approval by the Secretary of Defense to Use INDs. Use of an IND for force health protection requires approval of the Secretary of Defense.

4.2.1. A Commander of a Combatant Command shall submit a request through the Chairman of the Joint Chiefs of Staff, coordinated with the ASD(HA), the USD(Policy), Secretary of the Army as Executive Agent, and the DoD General Counsel. Such a request must document a confirmed, high threat for which the use of an IND is needed, consideration of the risks and benefits of use of the IND, and compliance with the requirements of this Directive.

4.2.2. The Secretary of the Army, as Executive Agent, in concert with the Commander of the Combatant Command involved and the ASD(HA), shall develop a specific treatment protocol for use of the IND. The protocol shall comply with 21 CFR Part 312 (reference (c)). The protocol shall be approved by the Army Surgeon General's Human Subjects Research Review Board (HSRRB), a duly constituted Institutional Review Board under 21 CFR Part 56 (reference (c)), prior to submission to the FDA for review under 21 CFR Part 312 (reference (c)). Unless the Secretary requests a waiver by the President, the protocol will provide for, consistent with 21 CFR Part 50 (reference (c)), the prior informed consent of members receiving the IND. If the request for use of the IND also includes a request for waiver of informed consent, the requirements of paragraphs 4.3. through 4.8., below, shall also apply.

4.3. Requests By the Secretary of Defense to the President for a Waiver of Informed Consent. Under 10 U.S.C. 1107 (reference (a)), only the President may grant a waiver of informed consent to use an IND for force health protection in connection with members' participation in particular military operations and only the Secretary of Defense may request that the President grant such a waiver.

4.3.1. Grounds for Request. The Secretary shall request a waiver only upon a determination that obtaining informed consent:

4.3.1.1. Is not feasible.

4.3.1.2. Is contrary to the best interests of the member.

4.3.1.3. Is not in the interests of national security.

4.4. Standards and Criteria for Requesting a Waiver of Informed Consent. In making a determination referred to in subparagraph 4.3.1.1. or 4.3.1.2., above, the Secretary shall apply, and in making a determination referred to in subparagraph 4.3.1.3., above, the Secretary will consider, the standards and criteria set forth in 21 CFR 50.23(d) (reference (c)). Those standards and criteria are:

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

4.4.2. 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.

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

4.4.4. Conditioning use of the IND 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.

4.4.5. A duly constituted institutional review board (IRB) established and operated in accordance with the equirements of paragraph 4.5., below, has reviewed and approved the IND protocol and the administration of the IND without informed consent.

4.4.6. The risks and benefits of using the IND are evaluated with consideration of:

4.4.6.1. The context in which the IND will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional.

4.4.6.2. The nature of the disease or condition for which the preventive or therapeutic treatment is intended.

4.4.6.3. Conditions that could alter the intended effects of the IND, to the extent any such data are available.

4.4.7. Applicable logistical record keeping systems are capable of tracking and will be used to track movement of the IND from supplier to the individual recipient.

4.4.8. 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 subparagraph 4.8.1.) concerning the IND, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

4.4.9. Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by subparagraph 4.4.8., above.

4.4.10. Medical records of members involved in the military operation will accurately document the receipt by members of any IND in accordance with FDA regulations, including 21 CFR part 312 (reference (c)).

4.4.11. The protocol provides for adequate follow-up to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

4.4.12. The Secretary of the Army, as Executive Agent, is pursuing drug development, including a timeline, and marketing approval, in accordance with FDA regulations, with due diligence.

4.4.13. The IND protocol may proceed subject to review by the FDA under reference (c) and a decision by the President on the informed consent waiver request.

4.4.14. Applicable DoD Components will provide training to the appropriate medical personnel and potential recipients on the specific IND to be administered prior to its use.

4.4.15. The Commander of the Combatant Command concerned 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.

4.4.16. The DoD Components will report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in subparagraph 4.4.15., above) that otherwise might affect the determination to use an IND without informed consent.

4.4.17. The Secretary of the Army, as Executive Agent, shall provide the public notice referred to in subparagraph 4.7.3., below.

4.4.18. Use of the IND without informed consent otherwise conforms with applicable law and DoD policy.

4.5. Institutional Review Board Approval. An Institutional Review Board (IRB), compliant with 21 CFR Part 56 (reference (c)), shall approve every protocol for the use of an IND for force health protection. The Army Human Subjects Research Review Board (HSRRB), under the Surgeon General of the Army, is designated as the IRB responsible for purposes of IRB activities under this Directive.

4.5.1. In any case in which a protocol proposes to include a waiver of informed consent, the following additional requirements shall be applicable to the HSRRB review and approval of the protocol.

4.5.1.1. The HSRRB must include at least three non-affiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the HSRRB) and shall be required to obtain any necessary security clearances. The HSRRB 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 non-affiliated members.

4.5.1.2. Minutes of the HSRRB meeting(s) at which the proposed protocol was discussed shall be provided to the Secretary of Defense and the FDA. The minutes shall be in sufficient detail to show attendance, actions taken, the votes taken (including number of members voting for, against, or abstaining), the reasons for requiring changes in or disapproving any portion of the protocol, and a written summary of the discussion of controversial issues and their resolution.

4.5.2. The HSRRB must review and approve:

4.5.3.1. The information sheet required by subparagraphs 4.4.8., above, and 4.8.1., below.

4.5.3.2. 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).

4.5.3.3. The adequacy of the information and plans for its dissemination to healthcare providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations.

4.5.3.4. An informed consent form as required by FDA regulations at 21 CFR part 50 (reference (c)) in those circumstances in which the protocol includes informed consent by some or all personnel involved.

4.6. Content of Request by the Secretary of Defense to the President. A request by the Secretary to the President for a waiver of informed consent shall be developed in consultation with the FDA. Upon submission by the Secretary of the waiver request to the President, a copy of the request shall be provided to the Commissioner of FDA. The content of the request shall at a minimum include:

4.6.1. A full description of the threat, including the potential for exposure. If the threat is a chemical, biological, or radiological weapon, the waiver request shall contain an analysis of the probability that the weapon will be used, the method or methods of delivery, and the likely magnitude of its affect on the exposed individuals.

4.6.2. Documentation of compliance with the requirements of the FDA regulations at 21 CFR 50.23(d) (reference (c)). If the request is based on the grounds identified in subparagraphs 4.1.1. or 4.1.2., the documentation will include a statement that certifies and a written justification that documents that each of the criteria and standards set forth in 21 CFR 50.23(d) (reference (c)) (which also appear at paragraph 4.4., above) have been met. If the Secretary finds it highly impracticable to certify that all such criteria and standards have been fully met because doing so would significantly impair the Department of Defense's ability to carry out the particular military mission, the Secretary will provide to the President a written justification that documents which criteria and standards have or have not been met, explains the reasons for not meeting those which have not been met, and provides additional justification why a waiver should be granted solely on the grounds identified in subparagraph 4.1.3., above.

4.6.3. Any additional information pertinent to the Secretary's determination, including the minutes of the HSRRB meetings at which the IND use was considered.

4.7. Action Required After Waiver of Informed Consent. Following a waiver of informed consent by the President, the DoD Components shall ensure proper implementation.

4.7.1. Monitoring

4.7.1.1. The DoD Components responsible for implementation shall conduct an ongoing review and monitoring to assess adherence to the standards and criteria under 21 CFR 50.23(d) (reference (c)) and adhere to any periodic reporting requirements specified by the President at the time of the waiver approval. The Secretary shall provide to the President any required reports, with a copy to the FDA Commissioner.

4.7.1.2. The DoD Inspector General shall conduct an ongoing review and monitoring to assess adherence to the standards and criteria under 21 CFR 50.23(d) (reference (c)).

4.7.2. Congressional Notification. The Secretary shall, as soon as practicable, make the Congressional notifications required by 10 U.S.C. 1107(f)(3)(B) (reference (a)).

4.7.3. Public Notification. The Secretary shall, as soon as practicable and consistent with classification requirements, issue a public notice in the Federal Register describing each waiver of informed consent determination and a summary of the most current scientific information on the products used, as well as other information the President determines is appropriate.

4.7.4. Changed Circumstances. The Secretary shall notify the President and the FDA Commissioner if the threat countered by the IND changes significantly or if significant new information on the IND is received.

4.7.5. Termination of Waiver. A waiver expires at the end of one year (or an alternative time not to exceed one year specified by the President) or upon notification by the Secretary to the President that the particular military operation creating the need for the use of the IND has ended, whichever is earlier.

4.7.6. Request for Renewal. A request by the Secretary for a renewal by the President of a waiver must meet the same criteria as the original request and shall include any new information available relevant to the standards and criteria under 21 CFR 50.23(d) (reference (c)).

4.8. Training and Risk Communication

4.8.1. Notice Requirement for IND Use. When using an IND for force health protection, the DoD Components shall provide prior notice to personnel receiving the drug or biological product of the following:

4.8.1.1. That it is an IND (including specific information on whether it is approved by FDA and/or whether it is unapproved for its applied use).

4.8.1.2. The reasons the IND is being used.

4.8.1.3. Information regarding the possible side effects of the IND, including any known side effects possible as a result of interaction of the IND with other drugs or treatments being administered to such personnel.

4.8.1.4. Other information as required to be disclosed by the FDA.

4.8.2. Information to Poviders for IND Use. The DoD Components shall ensure that healthcare providers who administer the IND or who are likely to treat members who receive the IND receive the information identified in subparagraphs 4.8.1.3. and 4.8.1.4., above.

4.8.3. Record Keeping on Use of IND and Notice Requirement. The DoD Components shall ensure that medical records of personnel who receive an IND accurately document the receipt of the IND and the notice required by subparagraph 4.8.1., above.

4.8.4. Ongoing Training and Health Risk Communication. The DoD Components shall provide ongoing training and health risk communication on the requirements of using an IND in support of a military operation to all military personnel, including those in leadership positions, during chemical and biological warfare defense training and other training, as appropriate. This ongoing training and health risk communication shall include general information about 10 U.S.C. 1107, E.O. 13139, and 21 CFR 50.23(d) (references (a) through (c)).

4.8.5. Special Additional Training and Health Risk Communication When Informed Consent Is Waived

4.8.5.1. If the President grants a waiver of informed consent, the DoD Components shall provide training to all military personnel conducting the waiver protocol and health risk communication to all military personnel receiving the specific investigational drug to be administered prior to its use.

4.8.5.2. The Secretary shall submit the training and health risk communication plans as part of the IND protocol submission to the FDA and the reviewing IRB. Training and health risk communication shall include at a minimum:

4.8.5.2.1. The basis for any determination by the President that informed consent is not or may not be feasible.

4.8.5.2.2. The means for tracking use and adverse effects of the investigational drug.

4.8.5.2.3. The benefits and risks of using the investigational drug.

4.8.5.2.4. A statement that the investigational drug is not approved (or not approved for the intended use).

4.8.5.3. The DoD Components shall keep operational commanders informed of the overall requirements of successful protocol execution and their role, with the support of medical personnel, in ensuring successful execution of the protocol.

4.9. INDs for Non-military Personnel. In any case in which an IND is used for force health protection for military personnel and subject to the same health risk are Emergency-Essential civilian employees (reference (e)) and contractor personnel performing essential contractor services (reference (f)) in conjunction with the military mission, the IND shall be available for protection of these non-military personnel under the same terms and conditions, except that the authority to waive informed consent under references (a) through (c) is inapplicable to these personnel.

## 5. RESPONSIBILITIES

5.1. The Assistant Secretary of Defense (Health Affairs), under the Under Secretary of Defense (Personnel and Readiness), shall have primary responsibility for policy under this Directive, is authorized to issue Instructions for implementation of, and grant exceptions otherwise authorized by law to, this Directive, and shall monitor implementation of this Directive and any implementing Instructions.

5.2. The Secretary of the Army shall serve as Executive Agent for the execution of policy under this Directive and any implementing Instructions.

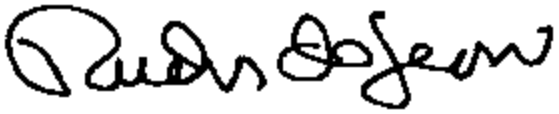
5.3. The Secretaries of the Military Departments shall implement requirements of this Directive, any implementing Instructions issued by the ASD(HA), and requirements established by the Secretary of the Army, as Executive Agent. In implementing an IND protocol, the Secretaries of the Military Departments shall strictly comply with requirements of the protocol.

5.4. The Chairman of the Joint Chiefs of Staff shall coordinate and direct activities of the Commanders of the Combatant Commands in the implementation of this Directive.

5.5. The Commanders of the Combatant Commands shall validate confirmed, high threats for which an IND is needed for force health protection, develop in coordination with the Executive Agent IND protocols, which will comply with requirements of this Directive, any implementing Instructions issued by the ASD(HA), and requirements established by the Executive Agent, execute IND protocols in strict compliance with their requirements, and implement other requirements of this Directive, any implementing Instructions, and requirements established by the Executive Agent.

6. EFFECTIVE DATE

This Directive is effective immediately.



Rudy de Leon
Deputy Secretary of Defense

Enclosures - 1
E1. References, continued

## E1. ENCLOSURE 1

## REFERENCES, continued

(e) DoD Directive 1404.10, "Emergency-Essential (E-E) DoD U.S. Citizen Civilian Employees," April 10, 1992

(f) DoD Instruction 3020.37, "Continuation of Essential DoD Contractor Services During Crises," November 6, 1990