

Medical Services

**Use of U.S. Food
and Drug
Administration-Regulated
Investigational
Products in
Humans Including
Schedule I
Controlled
Substances**

Headquarters
Department of the Army
Washington, DC
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UNCLASSIFIED

SUMMARY of CHANGE

AR 40-7

Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances

This major revision, dated 19 October 2009--

- Changes the title of the regulation to Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances.
- Implements DODD 3216.1, DODD 3216.02, and DODI 6200.2 (paras 1-5c, 1-5e, 2-2d, 4-1b, 4-4b(1), 4-5b(1), and 5-6).
- Updates information pertaining to clinical investigation protocols that use U.S. Food and Drug Administration-regulated investigational products (para 1-5d).
- Realigns and adds responsibilities relevant to the U.S. Army's use of U.S. Food and Drug Administration-regulated investigational products (chap 2).
- Identifies the required protocol approval and protocol submission requirements (chap 3).
- Reviews the nature of the U.S. Food and Drug Administration regulations and standards of regulated investigational products (chap 3).
- Reviews procedures for conduct of clinical research studies by Good Clinical Practice Standards and places them in one chapter (para 4-1).
- Adds sponsor responsibilities and timelines for reporting serious and unexpected adverse events associated with the use of investigational products to participating investigators and the U.S. Food and Drug Administration (para 4-4).
- Adds the responsibilities of the medical monitor as defined in DODD 3216.02 (para 4-5).
- Identifies exceptions to routine research uses of U.S. Food and Drug Administration-regulated investigational products (chap 5).
- Adds procedures related to the emergency use of an investigational new drug and unapproved devices (para 5-4).
- Outlines the uses and references of Schedule I controlled substances (chap 6).
- Includes information on the control of investigational drugs used to treat patients moving among U.S. Army Medical Centers and U.S. Army Medical Department Activities (app B).

- o Includes general information on the regulation of medical devices (app C).
- o Includes a Management Control Checklist (app D).
- o Replaces the term, "investigational drugs and devices" with "U.S. Food and Drug Administration-regulated investigational products" which includes biologics (throughout).
- o Makes administrative changes (throughout).


Medical Services

Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances

By Order of the Secretary of the Army:

GEORGE W. CASEY, JR.
General, United States Army
Chief of Staff

Official:


JOYCE E. MORROW
Administrative Assistant to the
Secretary of the Army

History. This publication is a major revision.

Summary. This regulation implements DODD 3216.1, DODD 3216.2, and DODI 6200.2. This regulation reaffirms Army compliance with U.S. Food and Drug Administration rules and regulations on the use of investigational products; includes citations for the use of International Conference on Harmonisation Guidelines for Good Clinical Practice in the use of investigational products; adds procedures for the control of investigational drugs used to treat patients moving among U.S. Army Medical Centers and U.S. Army Medical Department Activities; and updates office symbols and addresses.

Applicability. This regulation applies to

the Active Army, the Army National Guard/Army National Guard of the United States, and the U.S. Army Reserve, unless otherwise stated. It also applies to all personnel involved in clinical investigation programs, as well as to all Army Medical Department organizations involved in the use of investigational products in humans. During mobilization, the proponent may modify chapters and policies contained in this regulation.

Proponent and exception authority. The proponent of this regulation is The Surgeon General. The proponent has the authority to approve exceptions or waivers to this regulation that are consistent with controlling law and regulations. The proponent may delegate this approval authority, in writing, to a division chief within the proponent agency or its direct reporting unit or field operating agency, in the grade of colonel or the civilian equivalent. Activities may request a waiver to this regulation by providing justification that includes a full analysis of the expected benefits and must include formal review by the activity's senior legal officer. All waiver requests will be endorsed by the commander or senior leader of the requesting activity and forwarded through their higher headquarters to the policy proponent. Refer to AR 25-30 for specific guidance.

Army management control process.

This regulation contains management control provisions and identifies key management controls that must be evaluated (see appendix D).

Supplementation. Supplementation of this regulation and establishment of command and local forms are prohibited without prior approval from The Surgeon General (DASG-HSZ), 5109 Leesburg Pike, Falls Church, VA 22041-3258.

Suggested improvements. Users are invited to send comments and suggested improvements on DA Form 2028 (Recommended Changes to Publications and Blank Forms) directly to The Surgeon General (DASG-HSZ), 5109 Leesburg Pike, Falls Church, VA 22041-3258.

Distribution. This publication is available in electronic media only and is intended for command levels A, B, C, D and E for the Active Army, the Army National Guard/Army National Guard of the United States, and the U.S. Army Reserve.

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Glossary

Chapter 1 Introduction

1–1. Purpose

This regulation prescribes Department of the Army (DA) policies, procedures, and responsibilities for the use of U.S. Food and Drug Administration (FDA)-regulated investigational products, the use of FDA-approved drugs for unapproved indications in humans, and the use of U.S. Drug Enforcement Administration (DEA) Schedule I controlled substances in humans and animals where DA facilities, personnel, or financial support are used. This regulation implements, and is intended to be consistent with, FDA and DOD regulations. If these FDA or DOD regulations are changed to be more restrictive, there must be compliance with the more restrictive provisions.

1–2. References

Required and related publications and prescribed and referenced forms are listed in appendix A.

1–3. Explanation of abbreviations and terms

Abbreviations and special terms used in this regulation are explained in the glossary.

1–4. Responsibilities

See responsibilities chapter 2.

1–5. Overview

a. All references to FDA refer to the U.S. Food and Drug Administration. The FDA has statutory authority (under the Federal Food, Drug and Cosmetic (FD&C) Act as amended and other related Public Health Service Acts) to regulate scientific studies which are designed to develop evidence to support the safety and effectiveness of investigational drugs, biologic products, cosmetics, and medical devices, herein referred to as “FDA-regulated investigational products.” The FDA regulates the development of human products in accordance with Part 58, Title 21, Code of Federal Regulations (21 CFR 58), 21 CFR 210, 21 CFR 211, 21 CFR 312, 21 CFR 601, 21 CFR 812, and 21 CFR 814. Physicians and other qualified experts who conduct these studies must comply with applicable statutes and regulations intended to ensure the integrity of clinical data and to help protect the rights, safety, and welfare of human participants (21 CFR 50 and 21 CFR 56) enrolled in the studies.

b. The U.S. Army Medical Command (MEDCOM), in its missions as medical researcher, medical materiel developer, and health care provider, uses FDA-regulated investigational products. The following non-exhaustive list of representative DA trials identifies a variety of conditions for use of FDA-regulated investigational products.

(1) A Phase I clinical trial of an FDA-regulated investigational product sponsored by DA is conducted in a DA facility in the United States with DA participants.

(2) A clinical trial of a DA-sponsored FDA-regulated investigational product is conducted in a civilian facility inside and/or outside the United States (OCONUS) with other-than-DA participants.

(3) A DA organization is a partner in a clinical trial with another department or agency; academic, commercial, non-profit, not-for-profit entity or other organization; or other country. The DA organization may delegate or transfer specific duties to the other-than-DA organization(s) or country by legal agreements, but retains sponsorship of the FDA-regulated investigational product.

(4) A commercial organization contacts physicians at a U.S. Army Medical Center (MEDCEN) to participate in the conduct of a clinical trial of an FDA-regulated investigational product (for example, antibiotic or anti-cancer drug) for which the commercial organization is the sponsor.

(5) The DA MEDCENs, as members of National Cancer Institute Cooperative groups (for example, Southwest Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B) participate in multi-center trials that use FDA-regulated investigational products.

c. Department of the Army research using FDA-regulated investigational products in humans in any way and to any degree is subject to FDA regulations. The DA ensures protection of the rights and welfare of human participants in research using regulated investigational products by adhering to DOD and Army regulations) including 32 CFR 219; DODD 3216.02; AR 70–25 for research development, test, and evaluation (RDT&E) organizations; and AR 40–38 for military treatment facilities (MTFs)/dental treatment facilities (DTFs).

d. The FDA-accepted recommendations found in International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance/guideline documents are the basis for researchers, product developers, and leaders in planning and conducting medical research and in determining appropriate population selection for the conduct of research OCONUS.

e. The DA procedures to ensure humane use of animals in drug and device research are described in DODD 3216.1 and AR 40–33/SECNAVINST 3900.38C/AFMAN 40–401(I)/DARPAINST 18/USUHSINST 3203.

Chapter 2 Responsibilities

2-1. The Surgeon General/Commanding General, U.S. Army Medical Command

The Surgeon General (TSG)/Commanding General (CG), MEDCOM will—

- a.* Ensure that policies and procedures are developed that comply with regulations for investigations using FDA-regulated products in humans and animals, including Schedule I controlled substances.
- b.* Direct, as the CG, MEDCOM, the U.S. Army Medical Research and Materiel Command (USAMRMC) Clinical Investigation Regulatory Office (CIRO) to coordinate, monitor, review, and approve clinical investigations using other-than-DA-sponsored FDA-regulated products within an MTF/DTF.
- c.* Have, as TSG, the authority and sole responsibility within the Army to approve and provide regulatory oversight of all research involving human subjects regardless of the source of funding or the command, staff, or agency conducting the research. The Surgeon General may further delegate this authority.
- d.* Ensure compliance with all Federal, DOD, and Army regulations applicable to the conduct of investigations using FDA-regulated products.

2-2. Commander, U.S. Army Medical Research and Materiel Command

The Commander, USAMRMC will—

- a.* Serve on behalf of The Surgeon General as the sponsor's representative of DA-sponsored investigations conducted with FDA-regulated investigational products.
- b.* Exercise TSG-delegated approval authority for investigations conducted with DA-sponsored FDA-regulated investigational products; investigations conducted with other-than-DA-sponsored (for example, commercial pharmaceutical and device manufacturers) FDA-regulated investigational products in Army RDT&E facilities; and investigations involving the use of Schedule I controlled substances conducted or managed by an Army organization.
- c.* Maintain the Office of Research Protections (ORP).
- d.* Maintain the Human Subjects Research Review Board to ensure research involving human participants is in compliance with regulations governing such research (for example, 21 CFR 50, 32 CFR 219, DODD 3216.02, and AR 70-25).
- e.* Ensure the maintenance of an independent quality management program with adequate internal controls and oversight activities to support the use of FDA-regulated products.

2-3. Director, Division of Regulated Activities and Compliance, U.S. Army Medical Materiel Development Activity

The Commander, USAMRMC has delegated sponsor representative responsibilities to the Director, Division of Regulated Activities and Compliance (DRAC), U.S. Army Medical Materiel Development Activity (USAMMDA), a subordinate command of the USAMRMC. The Director, DRAC, acting as the sponsor's representative, will—

- a.* Ensure that all the sponsor's responsibilities, defined in 21 CFR 312, Subpart D, for FDA-regulated products are fulfilled. These responsibilities are executed through either USAMMDA or further delegation of responsibilities to organizations in USAMRMC or by agreement with external organizations (for example, contract research organizations or co-development partners).
- b.* Ensure the Commander, USAMMDA, in accordance with AR 70-57, is responsible for transferring sponsor responsibilities through appropriate clinical trial agreements, cooperative research and development agreements, memorandums of understanding, or memorandums of agreement through the appropriate Office of Research and Technology Applications (ORTA) or equivalent organizational element. The Director, DRAC will ensure that the FDA is notified when sponsor responsibilities are transferred.
- c.* Conduct post-marketing surveillance programs, in accordance with 21 CFR 314, 21 CFR 601, and 21 CFR 814, for DA-sponsored new drug applications (NDAs), biologics licensing applications (BLAs), 510(k)s, and premarket approval applications (PMAs). (See glossary for definition of 510(k).)
- d.* Ensure that training is available to investigators and monitor candidates so that they may be considered for selection by "training and experience" as required by the FDA.
- e.* Submit DA-sponsored investigational new drug (IND) and investigational device exemption (IDE) applications and amendments, NDAs, BLAs, PMAs, and 510(k)s to the FDA.
- f.* Maintain the sponsor's records for TSG-sponsored applications.
- g.* Utilize 21 CFR 312.32 for definitions, review of safety information, and IND safety reports and 21 CFR 812.150 for any reports regarding unanticipated adverse effect(s) associated with the use of an investigational device.
- h.* Ensure that clinical monitoring of DA-sponsored investigations using FDA-regulated investigational products is conducted in accordance with FDA regulations and guidance.
- i.* Serve as the primary contact for formal and informal communications with FDA.

j. Coordinate with other organizations that develop TSG-sponsored FDA-regulated products to ensure sponsor responsibilities are fulfilled.

2-4. Commanders of regional medical commands

Commanders of regional medical commands (RMCS) will—

a. Forward to the Commander, Army Medical Department Center and School (AMEDDC&S), CIRO (MCCS-GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234-5055, research protocols using sponsor-investigator sponsored and other-than-TSG-sponsored FDA regulated investigational products used within their commands except those involving Schedule 1 controlled substances.

b. Forward, through the CIRO, to the Office of Research Protections (MCMR-ZB-P), 504 Scott Street, Fort Detrick, MD 21702-5012, research protocols using DA-sponsored FDA-regulated investigational products within the RMC and all research protocols using Schedule I controlled substances.

c. Ensure compliance with all Federal, DOD, and Army regulations applicable to the conduct of research using FDA-regulated investigational products.

d. Ensure that DA medical researchers and developers using FDA-regulated investigational products in humans comply with FDA regulations and recommendations of the ICH (found in ICH guidance/guideline publications) to plan and conduct medical research and for appropriate population selection in the conduct of research OCONUS.

2-5. Commander, 18th Medical Command

The Commander, 18th Medical Command will—

a. Forward to the Office of Research Protections (MCMR-ZB-P), 504 Scott Street, Fort Detrick, MD 21702-5012, for review and approval, clinical protocols for FDA-regulated investigational products used within the 18th Medical Command, to include those involving Schedule I controlled substances, regardless of the sponsor.

b. Act as the approval authority for emergency procurement and use of investigational products in facilities that are organizationally a part of 18th Medical Command.

c. Ensure compliance with all Federal, DOD, and Army regulations applicable to the conduct of research using FDA-regulated investigational products.

d. Ensure that DA medical researchers and developers using regulated investigational products in humans comply with FDA regulations and recommendations of the ICH (found in ICH guidance/guideline publications) to plan and conduct medical research and for appropriate population selection in the conduct of research OCONUS.

2-6. Commanders of research, development, test, and evaluation organizations

Commanders, RDT&E organizations will—

a. Forward to the Office of Research Protections (MCMR-ZB-P), 504 Scott Street, Fort Detrick, MD 21702-5012, for review and approval, clinical protocols conducted or managed by their organization, using FDA-regulated investigational products to include those using Schedule I controlled substances, regardless of the sponsor.

b. Ensure that investigators coordinate with integrated product development teams and the clinical trial sponsor during preparation of DA-sponsored protocols.

c. Ensure that Federal, DOD, and Army regulations applicable to the conduct of research using FDA-regulated investigational products are met.

d. Ensure that DA medical researchers and developers using regulated investigational products in humans comply with FDA regulations and recommendations of the ICH (found in ICH guidance/guideline publications) to plan and conduct medical research and for appropriate population selection in the conduct of research OCONUS.

2-7. Army Medical Department Center and School, Clinical Investigation Regulatory Office

The AMEDDC&S, CIRO, acting as this focal point, will—

a. Review and forward to the ORP, clinical protocols to be conducted in a MEDCOM MTF/DTF involving—

(1) Department of the Army-sponsored FDA-regulated investigational products.

(2) The FDA-regulated investigational products funded or managed by RDT&E organizations.

b. Review and approve or disapprove for the CG, MEDCOM, clinical protocols using other-than-DA-sponsored FDA-regulated investigational products to be conducted in MEDCOM MTFs/DTFs.

c. Ensure that Federal, DOD, and Army regulations applicable to the conduct of clinical research using FDA-regulated investigational products are met and issue a letter of approval to the respective department of clinical investigation.

d. Ensure that DA medical researchers and developers using regulated investigational products in humans apply FDA regulations and recommendations of the ICH (found in ICH guidance/guideline publications) to plan and conduct medical research and for appropriate population selection in the conduct of research OCONUS.

e. Be the approving authority for emergency procurement of drugs, devices, and biologics used in the practice of medicine and use of investigational products in MEDCOM MTFs/DTFs.

2–8. Institutions, laboratories, and treatment facilities

a. All human subjects research supported or conducted by the DOD will be conducted under an assurance of compliance acceptable to the funding agency. Research performed at DOD facilities and funded by the DOD will have a DOD assurance of compliance.

b. Other-than-DOD institutions, laboratories, and treatment facilities conducting DOD-supported research involving human participants that do not have a Federal Wide Assurance (FWA) must obtain either an FWA or an assurance of compliance for human research participant protection with the DOD. The assurance requires that research investigators, Institutional Review Board (IRB) members and staff, and other relevant personnel maintain continuing knowledge of, and compliance with, Federal regulations, other applicable guidance, State and local law, and institutional policies for the protection of human participants in research.

2–9. Investigators

a. Investigators will be selected by the sponsor based on experience and qualifications to include appropriate licensing, credentialing, and privileging within the requirements of the respective research/medical practice organization.

b. Investigator’s responsibilities under 21 CFR 312, Subpart D are restated in Block 9 “Commitments” on FDA Form 1572 (Statement of Investigator). The investigator makes an attestation to abide by these responsibilities when he/she signs the form. The investigator’s commitments are—

(1) I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

(2) I agree to personally conduct or supervise the described investigation(s).

(3) I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes, and I will ensure that the requirements relating to obtaining informed consent in 21 CFR 50 and IRB review and approval in 21 CFR 56 are met.

(4) I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

(5) I have read and understand the information in the Investigator’s Brochure, including the potential risks and side effects of the drug.

(6) I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(7) I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with appropriate FDA regulations.

(8) I will ensure that an IRB that complies with the requirements of 21 CFR 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

(9) I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312.

c. Investigators will comply with all other requirements in 21 CFR, Subpart D.

d. Investigators will comply with all other requirements in 21 CFR 50, 21 CFR 54, and 21 CFR 312.

e. Investigator’s responsibilities for a clinical trial of devices are found in 21 CFR 812. Specifically, for device studies, the sponsor should develop an investigator’s agreement which includes the elements of 21 CFR 812.43(c) in lieu of an FDA Form 1572. The sponsor should have all investigators sign the agreement prior to participating in the study.

Chapter 3

Scientific and Institutional Review Board Approvals and Submission of Human Research Protocols to the U.S. Food and Drug Administration

3–1. General guidance

a. The IRB approval requires that all research protocols be scientifically sound. Research protocols must receive scientific and ethical review before official submission to the FDA and before research is initiated. (Protocols may be shared with the FDA in draft form for consultation before IRB review. This type of cooperative planning and preparation is encouraged by the FDA.) Ethical review is performed by at least the primary IRB (also referred to as the IRB of record). The IRB names vary by institution and include such names as— independent ethics committee, ethical review committee, independent ethics review committee, human use committee (HUC), or human use review committee. The task of the IRB is to safeguard the rights, safety, and well-being of all trial participants in accordance with AR

70–25 and AR 40–38. Investigators will provide evidence of current good clinical practices training for each individual identified on FDA Form 1572. The IRB will be comprised and function in accordance with 21 CFR 50, 21 CFR 56, and 32 CFR 219 and will be acknowledged in assurances of compliance adhered to by the commander or head of the facility at which the research protocol will be conducted. A second ethical review is performed on DOD research protocols by a headquarters level regulatory review organization.

b. A table listing the title and purpose of documents to be prepared and on file before the clinical phase of the trial commences may be found in the ICH’s “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance,” paragraph 8.2, as a reference for investigators.

c. The trial sponsor must include the human research protocol as part of the IND application, or IDE, submitted to the FDA. The requirements for information to be included in IND applications and IDEs are found in 21 CFR 312 and in 21 CFR 812, respectively. General information regarding the FDA regulation of medical devices is provided at appendix D of this regulation. The DRAC will participate in the planning and review of documents before submission to the IRB and FDA. Investigators will submit financial disclosure reports to study sponsors in accordance with 21 CFR 54. The IND or IDE records held by DA agencies will be maintained in accordance with applicable Federal regulations and AR 25–400–2.

3–2. Approval of human research protocols using The Surgeon General-sponsored U.S. Food and Drug Administration-regulated investigational products

a. Research conducted in an MTF/DTF may not begin until the protocol has been—

(1) Reviewed (scientifically and ethically) and approved at the first level that IRB endorsement can be given (that is, at the MTF/DTF where the investigation will be conducted or at the RMC of which the MTF/DTF is a part).

(2) Approved by the MTF/DTF commander and the RMC commander where the research will be conducted.

(3) Reviewed by the AMEDDC&S, Clinical Investigation Regulatory Office (MCCS–GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234–5055.

(4) Forwarded to Commander, USAMMDA (MCMR–UMR), Fort Detrick, MD 21702–9240.

(5) Reviewed and approved by the USAMRMC ORP in accordance with USAMRMC policy requirements specified in AR 70–25.

(6) Submitted to the FDA by the Director, DRAC as part of an IND application. Per FDA Form 1571 (Investigational New Drug Application), a clinical investigation may not begin until 30 days after FDA’s receipt of the new IND or IDE unless FDA notifies the sponsor that the study may begin.

b. Research conducted or managed by an RDT&E organization either within or outside of a DOD facility may not begin until the protocol has been—

(1) Reviewed (scientifically and ethically) and approved.

(2) Approved by the commander of the facility where the research will be conducted.

(3) Forwarded to Commander, USAMMDA (MCMR–UMR), Fort Detrick, MD 21702–9240.

(4) Reviewed and approved by the USAMRMC ORP in accordance with USAMRMC policy requirements specified in AR 70–25.

(5) Submitted to the FDA by the Director, DRAC acting as sponsor’s representative. Per FDA Form 1571, a clinical investigation may not begin until 30 days after FDA’s receipt of the new IND unless the FDA notifies the sponsor that the study may begin.

(6) Approved by the Director, DRAC who must determine that all of the sponsor’s responsibilities have been met before the study may begin.

3–3. Approval of human research protocols using other-than-Department of the Army-sponsored U.S. Food and Drug Administration-regulated investigational products

a. Research conducted in an MTF/DTF may not begin until the protocol has been—

(1) Reviewed (scientifically and ethically) and approved at the MTF/DTF where the investigation will be conducted or at the RMC of which the MTF/DTF is a part.

(2) Approved by the MTF/DTF commander and the RMC commander where the research will be conducted.

(3) Reviewed and approved by the AMEDDC&S, Clinical Investigation Regulatory Office (MCCS–GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234–5055.

b. Research conducted using RDT&E-managed resources may not begin until the protocol has been forwarded to the Office of Research Protections (MCMR–ZB–P), 504 Scott Street, Fort Detrick, MD 21702–5012 for review and approval.

3–4. Approval of human research protocols using radiopharmaceuticals

The human research protocol must be reviewed and approved by a radiation control committee established in accordance with the requirements of TB MED 525 in addition to the applicable protocol reviews noted above. (The

radiation control committee may function as an FDA-approved radioactive drug research committee under the auspices of 21 CFR 361.1.)

3-5. Submission of human research protocols using The Surgeon General-sponsored U.S. Food and Drug Administration-regulated products to the U.S. Food and Drug Administration

The human research protocol either as part of a new IND or IDE application, or as a subsequent research protocol within an approved IND or IDE, will be forwarded to the Director, DRAC who will submit it to the FDA. The Director, DRAC prepares and maintains records of amendments and communications with the FDA concerning TSG-sponsored INDs and IDEs.

3-6. Submission of human research protocols using other-than-The Surgeon General-sponsored U.S. Food and Drug Administration-regulated products to the U.S. Food and Drug Administration

The non-TSG sponsor for other-than-TSG-sponsored INDs and IDEs (usually a commercial pharmaceutical or device manufacturer) will submit the IND application or IDE to the FDA and will be responsible for compliance with Title 21 CFR 54, 56, 58, 210, 211, 312, 314, 610, and 812 requirements. Investigators must obtain for the non-TSG-sponsored products, the following for inclusion in the protocol review and approval process of the scientific review committee, IRB, and the USAMRMC ORP: a copy of the research protocol, the current Investigator's Brochure, the informed consent form, case report forms, and the curriculum vitae of investigators and subinvestigators listed on FDA Form 1572.

3-7. Submission of human research protocols using sponsor-investigator sponsored U.S. Food and Drug Administration-regulated products to the U.S. Food and Drug Administration

Refer to the glossary of this regulation for a definition of sponsor-investigator. An investigator who considers becoming a sponsor-investigator must obtain the written authorization from TSG with a justification for acting as a sponsor-investigator. If approval is granted, the sponsor-investigator must still coordinate with experienced sponsor offices either within or outside the MEDCOM.

a. An individual investigator may sponsor investigations (sponsor-investigator) using FDA-regulated investigational products in a DA MTF/DTF. A sponsor-investigator will fulfill all sponsor responsibilities to include acquiring all chain-of-command, scientific, IRB, and FDA approvals. The sponsor-investigator will submit the new IND application directly to the FDA. Per FDA Form 1571, a clinical investigation cannot begin until 30 days after FDA's receipt of the new IND unless the FDA notifies the sponsor that the study may begin. The sponsor-investigator will prepare and maintain records of all correspondence with the FDA.

b. If the sponsor-investigator is an active duty member or civilian employee of an organization within the purview of the CIRO, the sponsor-investigator must provide an informational copy of the IND or IDE submission and any subsequent correspondence with the FDA to the Clinical Investigation Regulatory Office (MCCS-GCI), Fort Sam Houston, TX 78234-5055.

c. The Commander, USAMRMC will assess the merits of proposed sponsor-investigator studies within the USAMRMC on a case-by-case basis. Because the USAMRMC includes a sponsor-representative organization (USAMMDA), the need for sponsor-investigator studies should be for exceptional circumstances. Prospective USAMRMC sponsor-investigators must coordinate their request through the Director, DRAC to justify why the existing sponsor functions at the USAMMDA cannot be used and to ensure that all required regulatory functions will be satisfied. Staffing documentation of the request for sponsor-investigator status through the Director, DRAC is required prior to seeking Commander, USAMRMC approval.

3-8. Approval of human research protocol amendments

According to 21 CFR 312.30(b)(1), "A sponsor shall submit a protocol amendment describing any change in a Phase I protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study" to the FDA for review. The change must also be approved by the IRB(s) with responsibility for review and approval of the study. According to 21 CFR 312.30(b)(2)(ii), a "protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c)." The Director, DRAC will submit research protocol amendments for TSG-sponsored INDs or IDEs to the FDA. Investigators must comply with the approved amended protocol.

Chapter 4 Human Research Protocol Conduct Using Good Clinical Practice Standards

4-1. General guidance

a. Good clinical practice is an ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible. Procedures for handling FDA investigational products in an RDT&E facility or in an MTF/DTF must comply with appropriate FDA regulations and apply the principles found in applicable FDA Guidance-for-Industry documents.

b. Clinical research protocols using FDA-regulated investigational products will be conducted in accordance with Title 21 CFR, Title 32 CFR, and Defense and Army regulations including DODD 3216.01, DODD 3216.02, DODI 6200.02, AR 40-38 (for clinical investigations), and AR 70-25 (for RDT&E research) to afford research participants protection of their rights and welfare.

c. Essential documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A list of the documents required for clinical trials can be found in the ICH's "Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance" chapter 8. These documents serve to demonstrate the compliance (of the investigator, sponsor, and monitor) with Good Clinical Practice standards and other applicable regulatory requirements. Essential documents will be retired in accordance with FDA regulations and policies of respective sponsors.

4-2. Sponsor monitoring of conduct of the human research protocol

In accordance with 21 CFR 312.56(a), it is the sponsor's responsibility to oversee the progress of a clinical trial and ensure that it is conducted, recorded, and reported in accordance with the protocol, standing operating procedures (SOPs), and study-specific SOPs. The clinical trial will be monitored as described in FDA regulations using the principles found in recommendations from the ICH's "Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance." The sponsor will coordinate the preparation of a monitoring plan with each investigator for all TSG-sponsored IND and IDE protocols using FDA-regulated investigational products.

4-3. Control and handling of U.S. Food and Drug Administration-regulated investigational products at regional medical commands and at military treatment facilities/dental treatment facilities

a. General. Investigational products are the property of the sponsor throughout the study. The MTF/DTF commander where the research is being conducted must establish procedures to ensure that basic essential information on investigational products is maintained and can be made available to all authorized personnel. In MTFs, the pharmacy is the appropriate location for investigational products. The pharmacy is responsible for the accountability of the investigational products to include storing, dispensing, and disposing of the investigational products in accordance with the investigator's written orders. The pharmacy and therapeutics committee (see AR 40-3) should act as the monitor of available information. As a minimum, information normally in the Investigator's Brochure (dosage, indications, expected effects, potential untoward effects, contraindications, storage requirements, and preparation and administration instructions) and names and telephone numbers of investigators and subinvestigators must be available to study personnel who administer investigational products. For studies involving blinded investigational products, procedures for breaking the blinding code must be stated in the human research protocol.

b. Drugs or biologics.

(1) A complete record on the disposition of each investigational product will be maintained by the pharmacy or appointed custodian. The IND record custodian must resolve discrepancies in inventory record balances and on-hand balances. The custodian must report unresolved discrepancies to the investigator and, if necessary, to the sponsor and to the FDA. The IND record must contain the following information:

- (a) Name of drug, dosage form, and strength (or proper identification if blinded).
- (b) Title of protocol under which the drug is used.
- (c) Signed copy of FDA Form 1572 with the name(s) of investigator(s).
- (d) Manufacturer or other source of drug.
- (e) Amount of drug and date received.
- (f) Perpetual inventory record of on-hand drug stocks.
- (g) Expiration date (if available).
- (h) Lot or control number.
- (i) Name(s) of participant(s) and drug, plus lot or control number for each dispensing.
- (j) Date(s) on which participant(s) receives drug and quantity dispensed.
- (k) Initials of dispensing official.

(2) Point of contact and procedures for emergency unblinding, if applicable.

(3) The pharmacy is the appropriate storage area for all investigational products in MTFs. Investigational products must be handled in the standard manner with respect to packaging, labeling, order receiving, profile maintenance,

inventory checks, and delivery. In addition to labeling requirements specified in AR 40–3 for dispensed medications, the immediate package of an IND must be labeled with the following statement: “Caution: New Drug – Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6(a)). Pre-established inventory accountability procedures with a clear audit trail must be maintained. The storage of investigational products must be separate from the regularly stocked drugs in the pharmacy and identified in such a way that minimizes the risk of being dispensed as a regularly stocked drug. Security requirements for storage of pharmaceuticals are identified in AR 40–61. Appendix B contains instructions for the control of investigational products used to treat patients moving among MEDCENS/U.S. Army Medical Department Activities (MEDDACs).

c. Devices.

(1) Storage, security, and recordkeeping requirements for investigational devices are determined based on the nature and use of the device. For clinical investigations involving investigational medical devices, a custodian of the device must be designated for maintaining accurate, complete, and current records relating to the investigator’s participation in the study. This includes records of receipt, use or disposition of a device that relate to the type and quantity of the device; the dates of its receipt and the batch number or code mark; the names of all persons who received, used, or disposed of each device; and why and how many units of the device have been returned to the sponsor, repaired, or been subjected to other disposition. Within MTFs, the chief of the clinical support division (or comparable person) shall maintain a listing of investigational devices in use within the hospital, their lot or control numbers, and the custodians for each device. In accordance with 21 CFR 812.5, the label of an investigational device or its immediate package must contain the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 21 CFR 801); the quantity of contents, if appropriate; and the following statement: “CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other packaging shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. The labeling of an investigational device must not contain any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(2) The custodian of an investigational device will establish an information file for the device. This information file will contain, as applicable—

(a) Investigator’s Brochure (or equivalent) to include the name of device (or proper identification if blinded), indications, expected effects, potential untoward effects, contraindications, and storage requirements.

(b) Preparation and administration instructions.

(c) Title of protocol under which device is used.

(d) Signed copy of Investigator’s Agreement with the name(s) of investigator(s).

(e) Manufacturer or other source of device.

(f) Amount of device(s) and date received.

(g) Perpetual inventory record of on-hand stocks of device.

(h) Expiration date (if available).

(i) Lot or control number.

(j) Name(s) of participant(s) and device, plus lot or control number for each dispensing of product.

(k) Date(s) on which participant(s) receives/uses device and quantity dispensed.

(l) Initials of dispensing official.

(m) Point of contact and procedures for emergency unblinding, if applicable.

d. Prescribing and dispensing.

(1) Personnel authorized prescribing privileges in accordance with AR 40–68 may prescribe INDs and devices. Non-physician prescribers must be appropriately privileged and approved by their local commanders to prescribe investigational new products. These prescribing limitations will be stated in the credentialing documentation.

(2) The pharmacy service or other designated investigational product or device custodian will dispense investigational products or devices as ordered on DD Form 1289 (DOD Prescription), DA Form 4256 (Doctor’s Orders) signed by the investigator or by a subinvestigator listed on FDA Form 1572 (for IND), or by authorized electronic prescription (for example, as generated by the Composite Health Care System or the AHLTA). A copy of the FDA Form 1572 will be located in the dispensing area (for example, in the pharmacy).

e. Administration of FDA-regulated investigational products. The investigator is responsible for providing the necessary information about basic pharmacology, storage, adverse effects, precautions, authorized prescribers, patient monitoring guidelines, and overall study objectives and procedures to properly credential and/or licensed nurses and other health care professionals designated to administer investigational products. This information is generally available in the Investigator’s Brochure for the specific IND. For investigational devices, users will be trained and have adequate knowledge of necessary calibration, application, and general use procedures for the device.

f. Radiopharmaceutical investigational new drugs and devices. The preferred area for storing radiopharmaceuticals is a nuclear pharmacy collocated with the nuclear medicine service. If a nuclear pharmacy is not available, radiopharmaceuticals can be kept in a designated secure storage area within the nuclear medicine department. The nuclear

pharmacy or nuclear medicine service will be responsible for proper recordkeeping, labeling, storage, and handling of the radiopharmaceuticals subject to appropriate regulations.

g. Research record retention period. The 21 CFR 812.140 requires that all research records involving an investigational device be kept until 2 years after the date on which the investigation is terminated or completed or the date the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol, whichever is later. Before disposing of the clinical records, the sponsor must be notified in writing.

4-4. Report of adverse events/experiences with U.S. Food and Drug Administration-regulated investigational new drugs

a. An adverse event/experience is defined in 21 CFR 312.32 and provided in the glossary of this regulation.

b. Procedures relating to the reporting of serious and unexpected IND adverse events/experiences as defined by 21 CFR 312.32 include—

(1) An investigator who observes or learns of a death, regardless of the presumed relationship to the investigational new product, must immediately notify the medical monitor (described in DODD 3216.02, para 4.4.3) and sponsor. The investigator must also submit required reports to the sponsor even if complete information is not yet available. Initial reports may be made by telephone; however, a written report will be provided by electronic mail or facsimile as soon as possible. Follow-up reports will be made as additional relevant information becomes available.

(2) An investigator must immediately consult with the study medical monitor and notify the sponsor of any adverse event/experience associated with the use of an IND that is alarming (that is, serious and unexpected), but not fatal. The investigator must also submit required reports to the sponsor even if complete information is not yet available. Initial reports may be made by telephone; however, a written report will be provided by electronic mail or facsimile as soon as possible. Followup reports will be made as additional relevant information becomes available.

(3) An investigator must promptly notify the sponsor of any serious adverse effect that is associated with the use of the drug, and there is a reasonable possibility that the experience may have been caused by the drug.

(4) For a TSG-sponsored IND or IDE, notification must be made to the sponsor's representative (Director, DRAC). The preferred method of notification is by e-mail to USAMRMCRegulatoryAffairs@amedd.army.mil. Reports may also be sent to the Commander, USAMMDA, (MCMR-UMR), 1430 Veterans Drive, Fort Detrick, MD 21702-9232 with telephonic communication to the DRAC at defense switched network (DSN) 343-0317/commercial 301-619-0317 and facsimile DSN 343-0197/commercial 301-619-0197.

(5) As required by 21 CFR 56.108(b)(1) and 21 CFR 312.66, the investigator will follow the written procedures of the approving IRBs for reporting unanticipated problems involving risks to human participants or others. For reporting to the USAMRMC ORP, call DSN 343-2165/commercial 301-663-2165. The facsimile number is DSN 343-7803/commercial 301-619-7803.

(6) As a minimum, investigators must collect the adverse event information requested on FDA Form 3500 (Med-Watch) and submit it to the study sponsor on protocol-specific case report forms or FDA Form 3500.

(7) For serious and unexpected adverse events/experiences judged by the sponsor's medical expert to be associated with the use of the IND, the sponsor must submit an IND safety report to the FDA. For an unexpected fatal or life-threatening experience associated with the use of the IND, this report will be made by telephone or facsimile as soon as possible, but not later than 7 calendar days after the sponsor's initial receipt of the information. For other serious and unexpected experiences associated with the use of the IND, the report must be submitted in writing within 15 calendar days of the sponsor's initial receipt of the information. An IND safety report made to the FDA by telephone or facsimile will be followed by a written IND safety report submitted within 15 calendar days of the initial telephone or facsimile report.

(8) The sponsor must notify all participating investigators of all IND safety reports.

(9) The sponsor must submit to the FDA, and all participating investigators, followup information to an IND safety report as soon as the relevant information is available.

4-5. Report of unanticipated and/or serious adverse device effects with U.S. Food and Drug Administration-regulated investigational products

a. Refer to the glossary of this regulation for the definition of unanticipated adverse device effect.

b. Procedures for reporting unanticipated adverse device effects—

(1) An investigator who observes an unanticipated adverse device effect must notify the medical monitor (described in DODD 3216.02, para 4.4.3) and the sponsor. An investigator must also submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect(s) occurring during an investigation as soon as possible, but not later than 10 working days after the investigator first learns of the effect (21 CFR 812.150). For a DA-sponsored device, this notification must be made to the sponsor's representative (Director, DRAC). The preferred method of notification is by e-mail to USAMRMCRegulatoryAffairs@amedd.army.mil. Reports may also be sent to the Commander, USAMMDA (MCMR-UMR), 1430 Veterans Drive, Fort Detrick, MD 21702-9232 with telephonic communication to the DRAC at DSN 343-0317/commercial 301-619-0317 and facsimile DSN 343-0197/commercial

301-619-0197. As required by 21 CFR 56.108(b)(1), the investigator must follow the written procedures of the approving IRB(s) for reporting unanticipated problems involving risks to human participants or others. For reporting to the USAMRMC ORP, call DSN 343-2165/commercial 301-663-2165 and facsimile at DSN 343-7803/commercial 301-619-7803.

(2) The sponsor must immediately conduct an evaluation. If the sponsor determines that the unanticipated adverse device effect presents an unreasonable risk to participants, the sponsor must terminate the study (or the parts of the study presenting the risk) not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first receives notice of the effect. If the serious adverse event is from a TSG-IND, this evaluation is made by USAMMDA Medical Affairs Division. The sponsor must also submit an evaluation report to the FDA and to all reviewing IRB(s) and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, additional reports must be submitted as requested by the FDA.

(3) If the device is a significant-risk device, resumption of the terminated study must not begin without both IRB and FDA approval.

(4) All other adverse events from IDE research must be reported to the IRB of record in accordance with local procedures. The IDE annual report submitted to the sponsor and the continuing review report submitted to the IRB of record must contain a compilation of all adverse events and the respective outcomes associated with the product during the course of the year.

4-6. Continuing review reports to Institutional Review Board(s)

In accordance with 21 CFR 56.109(f), the IRB of record must conduct continuing review of research at intervals appropriate to the degree of risk, but no less than once per year. The investigator is responsible for submitting to the IRB of record the required report of research activities prior to the scheduled review date as delineated by the IRB in the original approval memorandum. This report should include—

- a. A protocol summary and a status report (including findings) on the progress of the research,
- b. The number of participants accrued,
- c. A description of any adverse events or unanticipated problems involving risks to participants or others,
- d. Any withdrawal of participants from the research or complaints about the research,
- e. A summary of any recent literature,
- f. Amendments or modifications to the protocol since the last review,
- g. Reports on multi-center trials and any other relevant information,
- h. A copy of the current informed consent document, and
- i. A copy of the approved continuing review report. This report must be submitted to the second level of review having responsibility for review of the protocol.

4-7. Investigator reports to the sponsor

Investigators must furnish progress reports, safety reports, final reports, and financial disclosure reports to the sponsor (21 CFR 312.64). Investigators of TSG-IND shall use the ICH's "Guideline for Industry Structure and Content of Clinical Study Reports (E3)" for guidance on the content of the final reports of investigations.

4-8. Participants moving among U.S. Army Medical Centers/U.S. Army Medical Department Activities

The MEDCEN/MEDDAC investigators who receive patients on investigational new product protocols from other MEDCENS/MEDDACs will follow the procedures outlined in appendix B.

Chapter 5

Exceptions to Routine Research Uses of U.S. Food and Drug Administration-Regulated Investigational Products

5-1. Use of a marketed drug for an unapproved indication

a. Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner, when the intent is the practice of medicine, does not require the submission of an IND application. However, when a physician uses an approved drug for an unapproved indication and systematically records data on the drug's effects in order to substantiate or refute a claim of therapeutic efficacy for the unapproved indication, the physician is conducting a clinical investigation. In these situations, the physician-investigator must adhere to the requirements of AR 40-38 (for clinical investigations) or AR 70-25 (for RDT&E research).

b. According to 21 CFR 312.2, a clinical investigation of a drug product that is lawfully marketed in the United States must be conducted under an IND application, unless all of the following apply:

(1) The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used for any other significant change in the labeling of the drug.

(2) If the drug undergoing investigation is lawfully marketed as a prescription drug product, and the investigation is not intended to support any significant change in the advertising for the product.

(3) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

(4) The investigation is conducted in compliance with the requirements for institutional use review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50.

(5) The investigation is conducted in compliance with 21 CFR 312.7.

c. For DA-supported research in which the necessity for an IND application seems unclear or ambiguous, contact the sponsor's representative at USAMMDA.

5-2. Treatment use of an investigational new drug

Refer to 21 CFR 312.34 and 21 CFR 312.35.

a. A physician must contact the IND sponsor to obtain the drug if he/she is seeking approval for one-time use of an investigational drug for a patient where there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the intended patient's disease (a treatment IND). If the sponsor agrees to release the drug for treatment use, it is the sponsor's responsibility to obtain permission from the FDA to supply the drug to the requesting physician. The treating physician must wait 30 days after the sponsor submits the treatment protocol to the FDA unless the FDA approves the treatment use earlier. All phase 2 and 3 investigational drug trials are listed on the www.clinicaltrials.gov Web site.

b. Before the new drug can be used in an MTF, the physician must, through the IRB of record and the MTF commander, obtain the approval of the MEDCOM Commander or designee. Within MEDCOM MTFs, requests for treatment use of INDs must be directed to the Commander, AMEDDC&S, Clinical Investigation Regulatory Office (MCCS-GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234-5055, DSN 471-2511/9302. In cases where approval is granted, the CIRO will furnish copies to the Office of Research Protections (MCMR-ZB-P), 504 Scott Street, Fort Detrick, MD 21702-5012. Within 18th Medical Command, requests should be directed to Office of Research Protections (MCMR-ZB-P), 504 Scott Street, Fort Detrick, MD 21702-5012. Requests must include the patient's name; the diagnosis; the drug name, IND number, quantity, and source; the medical officer responsible for the patient; and the nature of the treatment use of the investigational product.

c. It is the responsibility of the treating physician to obtain approval of the appropriate clinical investigation committee and IRB for the use of the IND and to meet all applicable investigator responsibilities under 21 CFR 50, 56, and 312, Subpart D.

d. In situations where the one-time treatment use is approved, the treating physician must send a report summarizing the case to the CIRO, USAMRMC Office of Research Protections, and the sponsor of the IND. In addition to describing the circumstances and outcome of the IND use, the physician must include copies of any forms or reports furnished to a commercial manufacturer, to any other-than-DA agency, or to an individual in connection with the case.

5-3. Treatment use of an investigational device

Refer to 21 CFR 812.36. A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment IDE.

5-4. Emergency use of an investigational new drug and unapproved devices

When the need for an IND arises in an emergency situation that does not allow time for submission of a treatment IND, such use must be in accordance with 21 CFR 312.36. When the emergency situation requires the use of an unapproved device, the procedures listed below as specified in the FDA Guidance on IDE Policies and Procedures will be followed:

a. A physician who intends to treat a patient with an unapproved medical device in an emergency situation should conclude that—

(1) The patient has a life-threatening condition that requires immediate treatment,

(2) No generally acceptable alternative treatment for the condition exists, and

(3) Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

b. The physician will make the determination that the patient's circumstances meet the above criteria, assess the potential for benefit from the use of the unapproved device, and have substantial reason to believe that benefits will

exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining—

- (1) Informed consent from the patient or a legal representative.
- (2) Clearance from the institution as specified by their policies.
- (3) Concurrence of the IRB chairperson.
- (4) An independent assessment from an uninvolved physician.
- (5) Authorization from the IDE sponsor, if an approved IDE exists for the device.

c. After the emergency use occurs, the treating physician is responsible for ensuring that certain follow-up procedures occur. If an IDE exists for the device, the physician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation. If no IDE exists, the physician should submit a follow-up report on the use of the device to the IDE staff. This report should contain a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

5-5. Emergency procurement of drugs and biologicals from foreign suppliers

a. Emergency procurement of foreign drugs that have comparable characteristics to FDA-approved drugs. It is TSG policy that drugs used in an Army MTF will be approved by the FDA and procured from FDA-approved suppliers. However, it is recognized that situations may arise when a drug cannot be procured in a timely manner from an FDA-approved supplier, especially in an MTF located OCONUS. If an FDA-approved drug is unavailable from a U.S. supplier, drugs distributed by foreign suppliers may be procured provided one of the following circumstances exists:

(1) The drug is needed to save life, limb, or eyesight and the time required to procure the drug from a U.S. supplier would endanger the patient's well-being.

(2) The drug is needed to continue life-sustaining chronic therapy, and the time required to procure the drug from a U.S. supplier would interrupt such therapy and endanger the patient's well-being.

b. Drugs purchased from foreign suppliers. Such drugs must contain the same active ingredient(s) and be formulated in the same dosage form as the like product procured from a U.S. supplier. If the active ingredient or dosage form of a product procured from a foreign supplier is not available in the United States, the drug will be considered investigational, and the procedures described above for use of an investigational drug apply.

c. Procedures for emergency procurement of drugs from foreign suppliers.

(1) The chief, pharmacy services must initiate the request for purchase of a drug from a foreign supplier when professional judgment necessitates such a purchase.

(2) The MTF commander or designee must sign all purchase requests for drugs from a foreign supplier.

(3) The chief, pharmacy services must maintain a record of the use of drugs procured from a foreign supplier. A copy of this record must be forwarded to the Commander, Army Medical Department Center & School, Clinical Investigation Regulatory Office (MCCS-GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234-5055, within 5 working days after the drug is procured from the foreign supplier. For 18th Medical Command, the record must be forwarded to the Office of Research Protections (MCMR-ZB-P), 504 Scott Street, Fort Detrick, MD 21702-5012. A copy of the record must also be presented at the next regularly scheduled meeting of the MTF pharmacy and therapeutics committee. This record will consist of the drug's trade name, generic name, manufacturer, lot number, expiration date, amount, and source; a brief justification of why procurement of the drug from a foreign supplier was necessary; and an identifier for the patient (for example, initials or last four digits of the patient's social security number (SSN)) who received the drug procured from a foreign supplier.

d. Emergency procurement of new vaccines, devices, and biological products for the practice of medicine. Vaccines and other biological products may not be procured from foreign suppliers if the same vaccine or biological product is available from a U.S. supplier.

e. Products not available from U.S. suppliers. If there is a need to procure a vaccine or biological product that is not available from a supplier in the United States, the vaccine or biological product will be considered investigational and the procedures for use of an investigational drug apply.

5-6. Use of investigational new drugs and approved drugs for unapproved indications in deployed military situations (Force Health Protection)

Section 1107, Title 10, United States Code (10 USC 1107) describes specific requirements for use of investigational drugs and approved drugs for unapproved indications in military contingency operations. This statute applies whenever the Secretary of Defense requests or requires a member of the Armed Forces to receive an IND or a drug unapproved for its applied use. The implementing instructions for 10 USC 1107 are described in 21 CFR 50.23(d), Executive Order 13139 (Improving Health Protection of Military Personnel Participating in Particular Military Operations), and DODI 6200.02.

5-7. Emergency use authorization (Project BioShield Act)

a. Section 564 of the FD&C Act (21 USC 360bbb-3), which was amended by the Project BioShield Act of 2004

(Public Law 108–276), permits the Secretary, Department of Health and Human Services (DHHS) to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces with a specified biological, chemical, radiological, or nuclear agent or agents. Under Section 564, the Secretary, DHHS may allow medical countermeasures to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by such agents when there are no adequate, approved, and available alternatives to protect the American people or the U.S. Armed Forces.

b. Section 564(b)(1) of the FD&C Act provides that, before an emergency use authorization (EUA) may be issued, the Secretary, DHHS must declare an emergency based on one of the following grounds:

(1) A determination by the Secretary, Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a specified biological, chemical, radiological, or nuclear agent or agents;

(2) A determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to U. S. military forces of attack with a specified biological, chemical, radiological, or nuclear agent or agents; or

(3) A determination by the Secretary, DHHS of a public health emergency under Section 319 of the Public Health Service (PHS) Act that affects, or has the significant potential to affect, national security and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such agent or agents.

5–8. Documentation and reporting of emergency use of antivenins lacking U.S. Food and Drug Administration approval in deployed military situations

a. Highly poisonous pit vipers, cobras, and scorpions can be found in many areas to which military forces are deployed. Untreated snakebites can cause convulsions, paralysis, hemorrhage, and death. Scorpion stings affect the nervous system. The most appropriate treatment for significant snake or scorpion envenomation is species-specific antivenin administered by trained medical personnel. Antivenins used to treat envenomation by endemic species are often not FDA-approved products because they are made for, and used in, areas other than the United States. The military medical care system purchases and stocks these species-specific antivenins locally for local use. They are not imported to the United States and reissued. Usage reports of these antivenins will be made to the FDA under an IND held by TSG as a non-required precautionary measure.

b. Use of one of these IND antivenins requires specific reporting. To ensure reporting can be easily accomplished, it is important that the treatment is fully documented in the patient record. For each case when one of these products is ordered, the information in (1) through (7), below, must be provided to the pharmacy service. These data must be forwarded by the pharmacy service to the theatre pharmacy staff officer. Theatre pharmacy staff officers have the responsibility to pass these data in reports to Commander, USAMMDA (MCMR–UMR), Fort Detrick, MD 21702–9240 who will submit them in a timely fashion to the FDA at least annually.

(1) Full name and rank of the patient.

(2) Branch of Service of the patient.

(3) Last four (4) digits of the patient’s SSN.

(4) Antivenin product used.

(5) Quantity of product used (number of vials and total number of ml or total dose).

(6) Patient’s clinical outcome from the treatment.

(7) Provider name, rank, last four (4) of the SSN, and unit identification.

Chapter 6 Schedule I Controlled Substances

6–1. Clinical use of Schedule I controlled substances

a. Title 21 CFR 1301 requires the DHHS to review and comment on the scientific merit of the studies and qualifications of the investigators conducting research with Schedule I controlled substances and drugs and to report this information to the DEA.

b. Title 21 USC 5.10 re-delegates to the FDA commissioner the function of determining the qualifications and competency of investigators wishing to conduct research with controlled substances and drugs listed in Schedule I and the merits of the research protocol. The commissioner assigns this responsibility to controlled substance staff within the Center for Drug Evaluation and Research (CDER).

c. References include the Controlled Substances Act of 1970, as amended (primarily 21 USC 823(f), 21 CFR 5, and 21 CFR 1301).

d. For approval to use a Schedule I controlled substance in human participants, a protocol must be submitted for

review and approval as outlined above for FDA-regulated investigational products. A statement of the security, audit, and control provisions for the Schedule I controlled substance must accompany the protocol and IND submissions (for example, the Investigator's Brochure will describe security requirements).

e. The IND sponsor must provide the investigator with the following statement: "I hereby certify that on (date), pursuant to 21 USC 355(i) and 21 CFR 130.3 I, (name and address of IND sponsor) submitted an Investigational New Drug application to the Food and Drug Administration for (name of investigational drug) (date) (signature of applicant)."

f. The statement must be forwarded in triplicate by the investigator along with a DEA Form 225 (Drug Enforcement Administration Certificate of Registration) to the Drug Enforcement Administration, Department of Justice, P.O. Box 28083, Central Station, Washington, DC 20038-8083.

6-2. Nonclinical use of Schedule I controlled substances

a. In order to conduct nonclinical animal research with Schedule I controlled substances, the investigator must submit DEA Form 225 along with three copies of the research protocol to the Drug Enforcement Administration, Department of Justice, P.O. Box 28083, Central Station, Washington, DC 20038-8083.

b. The research protocol must provide the following information:

- (1) Investigator's name, address, and current DEA registration number, if any.
- (2) Institutional affiliation of the researcher.
- (3) Qualifications of the investigator, including curriculum vitae and an appropriate list of publications.
- (4) Title of the study.
- (5) Statement of the research purpose.
- (6) Name and amount of controlled substance(s) involved.
- (7) Description of the research to include the species and number of research animals, dosage to be administered, route and method of administration, and duration of the project.
- (8) Location where the research will be conducted.
- (9) Statement of security provisions for storing the controlled substance(s) in order to prevent diversion.
- (10) Proof of institutional approval to conduct the research.
- (11) Indication of an approved, funded grant, if any.

c. The investigator will also comply with the provisions of AR 40-33/SECNAVINST 3900.38C/AFMAN 40-401(1)/DARPAINST 18/USUHSINST 3203.

Appendix A References

Section I

Required Publications

This section contains no entries.

Section II

Related Publications

A related publication is a source of additional information. The user does not have to read it to understand this regulation. Army regulations are available online at <http://www.apd.army.mil>. DOD directives and instructions are available at <http://www.dtic.mil/whs/directive>. Codes of Federal Regulations are available at <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>.

AR 11-2

Management Control

AR 25-400-2

The Army Records Information Management System (ARIMS)

AR 40-3

Medical, Dental, and Veterinary Care

AR 40-33/SECNAVINST 3900.38C/AFMAN 40-401(1)/DARPAINST 18/USUHSINST 3203

The Care and Use of Laboratory Animals in DOD Programs

AR 40-38

Clinical Investigation Program

AR 40-61

Medical Logistics Policies and Procedures

AR 40-68

Clinical Quality Management

AR 70-25

Use of Volunteers as Subjects of Research

AR 70-57

Military-Civilian Technology Transfer

DODD 3216.1

Use of Laboratory Animals in DOD Programs

DODD 3216.02

Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research

DODI 6200.02

Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs

TB MED 525

Control of Hazards to Health from Ionizing Radiation Used by the Army Medical Department (Available at <http://chppm-www.apgea.army.mil>.)

Executive Order 13139, 30 September 1999

Improving Health Protection of Military Personnel Participating in Particular Military Operations. (Available at <http://www.gpoaccess.gov/fr/index.html>.)

21 CFR 5

Organization

21 CFR 50

Protection of Human Subjects

21 CFR 54

Financial Disclosure by Clinical Investigators

21 CFR 56

Institutional Review Boards

21 CFR 58

Good Laboratory Practice for Nonclinical Laboratory Studies

21 CFR 210

Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs, General

21 CFR 211

Current Good Manufacturing Practice for Finished Pharmaceuticals

21 CFR 312

Investigational New Drug Application

21 CFR 314

Applications for FDA Approval to Market a New Drug

21 CFR 601

Licensing

21 CFR 610

General Biological Products Standards

21 CFR 801

Labeling

21 CFR 812

Investigational Device Exemptions

21 CFR 814

Premarket Approval of Medical Devices

21 CFR 1301

Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances

21 CFR 50.23

Exception from General Requirements

21 CFR 56.102

Definitions

21 CFR 56.104

Exemptions from IRB Requirement

21 CFR 56.108

IRB Functions and Operations

21 CFR 56.109

IRB Review of Research

21 CFR 130.3
Definitions and Interpretations

21 CFR 312.2
Applicability

21 CFR 312.3
Definitions and Interpretations

21 CFR 312.7
Promotion and Charging for Investigational Drugs

21 CFR 312.23
IND Content and Format

21 CFR 312.30
Protocol Amendments

21 CFR 312.32
IND Safety Reports

21 CFR 312.34
Treatment Use of an Investigational New Drug

21 CFR 312.35
Submission for Treatment Use

21 CFR 312.36
Emergency Use of an Investigational New Drug (IND)

21 CFR 312.56
Review of Ongoing Investigations

21 CFR 312.60
General Responsibilities of Investigators

21 CFR 312.61
Control of the Investigational Drug

21 CFR 312.62
Investigator Recordkeeping and Record Retention

21 CFR 312.64
Investigator Reports

21 CFR 312.66
Assurance of IRB Review

21 CFR 312.68
Inspection of Investigator's Records and Reports

21 CFR 312.69
Handling of Controlled Substances

21 CFR 361.1
Radioactive Drugs for Certain Research Uses

21 CFR 812.3
Definitions

21 CFR 812.5

Labeling of Investigational Devices

21 CFR 812.18

Import and Export Requirements

21 CFR 812.36

Treatment Use of an Investigational Device

21 CFR 812.43

Selecting Investigators and Monitors

21 CFR 812.140

Records

21 CFR 812.150

Reports

21 CFR 1308.11

Schedules of Controlled Substances, Schedule I

32 CFR 219

Protection of Human Subjects

32 CFR 219.102

Definitions

45 CFR 46

Protection of Human Subjects

10 USC 1107

Notice of use of an investigational new drug or a drug unapproved for its applied use (Available at <http://uscode.house.gov/search/criteria.shtml>.)

21 USC 321

Federal Food, Drug and Cosmetic Act, Chapter 9, Definitions (Available at searchable database <http://uscode.house.gov/search/criteria.shtml>.)

21 USC 355

Federal Food, Drug and Cosmetic Act, Chapter 9, Drugs and Devices, New Drugs (Available at searchable database <http://uscode.house.gov/search/criteria.shtml>.)

21 USC 360bbb-3 (Section 564 of the FD& C Act)

Authorization for Medical Products for Use in Emergencies (Available at searchable database <http://uscode.house.gov/search/criteria.shtml>.)

U.S. Food and Drug Administration

Guidance on IDE Policies and Procedures (Available at searchable database <http://uscode.house.gov/search/criteria.shtml>.)

U.S. Food and Drug Administration Information Sheets

Guidance for Institutional Review Boards and Clinical Investigators (Available at <http://www.fda.gov/oc/ohrt/irbs/default.htm>.)

U.S. Food and Drug Administration

ICH Guidance for industry E6 Clinical Practice: Consolidated Guidance (Available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf>.)

U.S. Food and Drug Administration

ICH Guidance for Industry Structure and Content of Clinical Study Reports (E3) (Available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129456.pdf>.)

National Bioethics Advisory Commission

Report of 30 April 2001 entitled, "Ethical and Policy Issues in Research Involving Human Participants" (Available at <http://bioethics.georgetown.edu/nbac/pubs.html>.)

National Institutes of Health, Office for Protection from Research Risks

Protecting Human Research Subjects, Institutional Review Board Guidebook (Available at http://www.hhs.gov/ohrp/irb/irb_guidebook.htm.)

Section III

Prescribed Forms

This section contains no entries.

Section IV

Referenced Forms

Unless otherwise indicated, DA forms are available on the APD Web site <http://www.apd.army.mil> and DD forms are available on the OSD Web site <http://www.dtic.mil/whs/directives/infomgt/formsprogram.htm>.

DA Form 11–2–R

Management Control Evaluation Certification Statement

DA Form 2028

Recommended Changes to Publications and Blank Forms

DA Form 4256

Doctor's Orders (Available through normal forms supply channels.)

DD Form 1289

DOD Prescription (Available through normal forms supply channels.)

DEA Form 225

Drug Enforcement Administration Certificate of Registration (Available from the Drug Enforcement Administration, Department of Justice, P.O. Box 28083, Central Station, Washington, DC 20038–8083.)

FDA Form 1571

Investigational New Drug Application (IND) (Available at <http://www.fda.gov>.)

FDA Form 1572

Statement of Investigator (Available at <http://www.fda.gov>.)

FDA Form 3500

MedWatch: For Voluntary Reporting by Health Care Professionals of Adverse Events and Product Problems (Available at <http://www.fda.gov>.)

NIH Form 2564

Investigational Agent Accountability Record (Available at <http://ctep.cancer.gov>.)

Appendix B

Control of Investigational Drugs Used to Treat Patients Moving Among U.S. Army Medical Centers and U.S. Army Medical Department Activities

B–1. Basic principles

a. This appendix generally refers to the transfer of patients enrolled in oncology treatment protocols from a MEDCEN within an RMC to a MEDDAC within that same RMC. However, there are some situations in which patients are transferred between RMCs.

b. Compliance with regulations on use, storage, and control of INDs outlined in this regulation is important because interstate shipment of all INDs is subject to Federal regulation by the FDA.

c. The physician listed as investigator on the investigational drug protocol submitted to the CIRO is responsible for the conduct of that protocol and for carrying out administrative requirements (for example, submission of continuing review reports) as outlined in this regulation.

d. The CIRO must be made aware of any extension of an investigational drug study to an additional MTF.

e. Review and approval of the investigational protocol by an RMC's scientific and ethical review committees (for example, clinical investigation committee) for a MEDDAC supported by the MEDCEN fulfills the FDA requirements for institutional review. Local commanders may require additional review at their discretion.

f. If a patient enrolled in an IND protocol transfers to an MTF that has functioning scientific and ethical review committees, the protocol will require review and approval at the gaining MTF. Investigators should initiate the review process early in the discharge planning process. Gaining facilities should have procedures in place that allow continuation of investigational therapy through the duration of the review process.

B-2. Procedure

When a patient agrees to participate with a treatment protocol involving an IND and transfers to another MEDCEN/MEDDAC or returns to the referring MEDCEN/MEDDAC, the following will be accomplished:

a. The investigator or designee from the MEDCEN/MEDDAC referral service (for example, the hematology/oncology service) will contact the gaining physician by telephone. They will discuss the patient's treatment follow up as well as the requirements of the FDA and this regulation pertaining to IND use. The investigator will inform the CIRO of the extension of an IND study to an additional MTF, the title of the study, and name of the MTF physician who will be in charge of continuing the patient's therapy. The gaining physician becomes a subinvestigator on the protocol.

b. The referring physician will mail the gaining physician a copy of the patient's medical records, a copy of the informed consent forms, a letter of instructions, a copy of the investigational protocol, a copy of the Investigator's Brochure, and FDA Form 1572.

c. The gaining physician completes FDA Form 1572 and returns it to the chief of the referring service who maintains the FDA Form 1572 in the protocol file for reference. The referring investigator will forward the name and curriculum vitae of the gaining physician to the Commander, AMEDDC&S, Clinical Investigation Regulatory Office (MCCS-GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234-5055 and to the appropriate agencies (for example, the National Cancer Institute) for inclusion on FDA Form 1572. The submission should also include the names of the gaining MTF's deputy commander for clinical services, the supervising chief of the department of medicine, the chief of pharmacy services, and the chief of the clinical investigation department (if one is formed at the MTF) to arrange for the patient to receive the investigational drug.

d. Upon receiving a request for an IND signed by an authorized physician, the referring pharmacy dispenses a supply of the IND and ships (requiring signature receipt) it to the gaining pharmacy chief with a copy of the investigational protocol and drug information, including possible adverse reactions or antidote procedures.

e. The gaining pharmacy will store the IND(s) until dispensing to the patient and will also provide appropriate drug-use counseling to the patient, with advice from the referral pharmacy as appropriate.

f. When an additional supply of the IND(s) is needed, the gaining pharmacy will notify the referring pharmacy. The medication will be shipped (requiring signature receipt) to the gaining pharmacy where it will be handled as indicated in paragraph d above.

g. If treatment is discontinued, the gaining physician will notify the pharmacy so that any remaining INDs may be returned to the referring pharmacy service.

h. The gaining physician must provide the MEDCEN/MEDDAC referral service with semiannual follow-up information regarding the patient's progress. Flow sheets for this purpose will be provided by the referring MEDCEN/MEDDAC. Follow-up information will be included in the referring MEDCEN/MEDDAC's clinical-investigation annual progress report for the particular study.

i. The MEDCEN/MEDDAC referral service (for example, the hematology-oncology service) is responsible for the following:

- (1) Maintenance of all records pertaining to the clinical investigation protocol.
- (2) Periodic follow-up evaluation of the patients, as required by the protocol.
- (3) Telephonic consultation services, as needed, for the gaining physician.
- (4) Pharmacy consultation services, as needed, for the gaining physician.

j. If the gaining physician leaves the MTF (for example, transfer, deployment, or separation), he/she must notify the referring MEDCEN/MEDDAC investigator of the planned departure in sufficient time to ensure continuity of patient care. The replacement physician should also take the actions described in i(1) through i(4), above. The referring MEDCEN/MEDDAC investigator should correspond with the National Institutes of Health (NIH) or any research sponsor and remove the name of the departing physician from the FDA Form 1572 as one of the subinvestigators and add the name of the new physician. The investigator must also notify the Commander, AMEDDC&S, Clinical

Investigation Regulatory Office (MCCS–GCI), 1608 Stanley Road, Fort Sam Houston, TX 78234–5055 of the removal and/or addition of a subinvestigator.

k. If the patient moves away from the MTF, the MTF physician will notify the referring MEDCEN/MEDDAC investigator and decide whether or not to extend the study to the patient’s new MTF or to terminate the patient’s enrollment in the protocol. This must be done with sufficient time to ensure appropriate patient care.

l. For NIH-sponsored INDs, the referring MEDCEN/MEDDAC pharmacy will prepare and forward NIH Form 2564 (Investigational Agent Accountability Record) to the gaining MTF to document the mailing of the IND from the referring MEDCEN/MEDDAC to the gaining MTF. The gaining MTF pharmacy will use this form for drug accountability and will send a photocopy of the completed form back to the referring MEDCEN/MEDDAC when reordering or returning medications. An inventory form provided by the study sponsor may be used as an alternate to NIH Form 2564.

m. Records of an investigator’s participation in the research protocol must be retained in accordance with the procedures identified in paragraphs 5–4 and 5–7.

n. For questions regarding the proper use of NIH Form 2564, consult the hematology/oncology pharmacist at the referring MEDCEN/MEDDAC.

Appendix C Medical Devices

C–1. Basic principles

The purpose of this appendix is to provide general information on the FDA regulation of medical devices. In addition, this appendix will provide references to additional sources of information. Medical devices range from simple tongue depressors and bedpans to laser surgical devices and complex programmable pacemakers with microchip technology. Medical devices also include *in vitro* diagnostic device (IVD) products, such as general purpose lab equipment, test kits that may include monoclonal antibody technology, and reagents. In addition, certain electronic-radiation-emitting products with medical applications and claims meet the definition of a medical device. Section 201(h) of the FD&C Act, codified at 21 USC 321(h) defines the term “device,” and the definition is provided in the glossary.

C–2. Device advice Web page

The Device Advice Web page located at <http://www.fda.gov/cdrh/index.html> provides general information regarding the regulation of medical devices. This Web page is in a question-and-answer format to help users find information in an efficient manner. This resource is also hyperlinked to more specific guidance documents and regulations to allow users to access detailed information regarding a given topic. Topics discussed within the Device Advice Web page include device classes, how to obtain market clearance, premarket notifications (510(k)s), premarket approval, IDE, significant and nonsignificant risk (NSR) device studies, good manufacturing practices and quality systems, and medical device reporting.

C–3. “Guidance on investigational advice exemption policies and procedures”

The document, “Guidance on IDE Policies and Procedures” provides the FDA’s current guidance on IDE policies and procedures. It includes guidance regarding changes in device regulation as a result of the Food and Drug Administration Modernization Act (the Modernization Act). The Modernization Act, enacted 21 Nov 1997, amended the FD&C Act (21 USC 301) relating to the regulation of food, drugs, devices, and biological products. “Guidance on IDE Policies and Procedures” is available at <http://www.fda.gov/cdrh/ode/idepolicy.html>. This document also addresses emergency use of unapproved devices.

C–4. Investigational Advice Exemption Regulation — 21 CFR 812

A full text version of 21 CFR 812 is available at http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr812_00.html.

C–5. Significant and nonsignificant risk investigations

The IRBs are required to make a determination of risk for devices studied in clinical trials. The FDA includes in their “1998 Update to Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators” examples of NSR/significant risk (SR) devices to assist sponsors and IRBs in making NSR/SR determinations. The lists include many commonly used medical devices and are available at <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk>. Inclusion of a device in the NSR category should not be viewed as a conclusive determination because the proposed use of a device in a study is the ultimate determinant of the potential risk to participants. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

C–6. Regulating *in vitro* diagnostic device studies

The FDA Guidance Document on regulating IVD studies is located at Web site: <http://www.fda.gov/cdrh/comp/ivdreg>.

html. The guidance explains how the Office of Compliance, Division of Bioresearch Monitoring, in conjunction with the Office of Device Evaluation (ODE), interprets and enforces the statute and regulations for investigational studies that involve the use of IVDs. Of particular concern for medical care and research is the requirement to file an IDE if the IVD is to be used for the purpose of diagnosing a disease. The IVD will be labeled with the statement: "Caution-Investigational Use. Limited by Federal (or United States) law to investigational use." If the IVD is not to be used for medical diagnosis, the IVD label and all laboratory reports from use of the IVD must be clearly marked with the phrase, "For research purposes only."

Appendix D Management Control Checklist

D-1. Function

The function covered by this checklist is the administration of the use of INDs and devices and the use of Schedule I controlled substances.

D-2. Purpose

The purpose of this checklist is to assist assessable unit managers and Management Control Administrators in evaluating the key management controls as required by AR 11-2. It is not intended to cover all controls.

D-3. Instructions

Answers must be based on the actual testing of key management controls (for example, document analysis, direct observation, sampling, simulation, auditing, other). Answers that indicate deficiencies must be explained and corrective action indicated in supporting documentation. These management controls must be evaluated at least once every three years. Certification that this evaluation has been conducted must be accomplished on DA Form 11-2-R (Management Control Evaluation Certification Statement).

D-4. Test questions

- a. Is AR 40-7 readily available for reference?
- b. Is the Investigator's Brochure (drug or device information) available?
- c. Are annual progress reports required by the sponsor in accordance with 21 CFR 316.64?
- d. Are continuing review reports required by the IRB of record submitted in a timely manner and in accordance with 21 CFR 56.108(a)?
- e. Are research protocols complete with background, hypothesis, objectives, military significance and methodology and in DA or ICH E6 formats as appropriate?
- f. Are literature references cited to support the research protocol?
- g. Do animal-use protocols include animal-use approval, justification for animal/species use, description of animal facilities, and evidence of compliance?
- h. Is there evidence that the sponsor has provided clinical monitoring of the IND or device research protocol in accordance with 21 CFR 312 or 21 CFR 812.46, respectively, and the ICH "Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance"?
- i. Is there compliance with the requirements for the protection of human participants identified in 21 CFR 50, 32 CFR 219, and AR 70-25?
- j. Does the hospital or research facility have appropriate standing operating procedures for the conduct of clinical trials? As a minimum, procedures should be available for—
 - (1) Scientific review of research protocols.
 - (2) Local human use review of research protocols.
 - (3) Training and education of research staff in Good Clinical Practice.
 - (4) Control and accountability of investigational products.
 - (5) Maintenance of regulatory files.
 - (6) Laboratory procedures (appropriate certification).
 - (7) Study-specific procedures.
 - (8) Adverse event reporting.
 - (9) Periodic reporting and final reports.
 - (10) Informed consent process.
 - (11) Participant recruitment.
 - (12) Participant record maintenance.
- k. Are procedures in place for emergency use of investigational products?

l. Are clinical trial agreements or other documents available to support responsibilities of investigators and sponsors?

m. Are procedures in place to ensure that participation in research does not conflict with 10 U.S.C 980?

n. Are final reports submitted at the conclusion of research activities?

o. For activities that use Schedule I controlled substances, are procedures in place to ensure the following:

(1) Has DEA Form 225 been completed?

(2) Is the Certificate of Registration available?

(3) Are the controlled substances correctly stored?

(4) Are security measures evident?

(5) Are dispensing records maintained correctly?

(6) Do only appropriate personnel have access?

(7) Can only authorized investigator(s) prescribe the controlled substance(s)?

(8) Do written records provide an audit trail of receipt, disposal, inventory, and distribution?

D-5. Supersession

This checklist is the initial management control checklist for Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans including Schedule 1 Controlled Substances.

D-6. Comments

Help to make this a better tool for evaluating management controls. Submit comments to: Commander, USAMMDA (MCMR-UMR), Fort Detrick, MD 21702.

Glossary

Section I Abbreviations

AMEDDC&S

Army Medical Department Center and School

AR

Army regulation

BLA

biologics license application

CDER

Center for Drug Evaluation and Research

CFR

Code of Federal Regulations

CIRO

Clinical Investigation Regulatory Office

DA

Department of the Army

DC

District of Columbia

DEA

Drug Enforcement Administration

DHHS

Department of Health and Human Services

DOD

Department of Defense

DODD

Department of Defense Directive

DODI

Department of Defense Instruction

DRAC

Division of Regulated Activities and Compliance

DSN

defense switched network

DTF

dental treatment facility

EUA

emergency use authorization

FDA

Food and Drug Administration

FD&C

Federal Food, Drug, and Cosmetic Act

FWA

Federal Wide Assurance

FR

Federal Register

GCP

good clinical practice

GPO

Government Printing Office

HHS

Health and Human Services

HUC

human use committee

ICH

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IDE

investigational device exemption

IND

investigational new drug

IRB

Institutional Review Board

IVD

in vitro diagnostic device(s)

MEDCEN

U.S. Army Medical Center

MEDDAC

U.S. Army Medical Department Activity

MD

Maryland

MTF

military treatment facility

NBAC

National Bioethics Advisory Commission

NDA

new drug application

NIH

National Institutes of Health

NSR

nonsignificant risk

OCONUS

outside continental United States

ODE

Office of Device Evaluation (of the Food and Drug Administration)

ORP

Office of Research Protections

ORTA

Office of Research and Technology Applications

P.O.

post office

PHS

Public Health Service

PMA

premarket approval application

RDT&E

research, development, test, and evaluation

RMC

regional medical command

SOP

standing operating procedure

SR

significant risk

SSN

social security number

TSG

The Surgeon General

TX

Texas

U.S.

United States

USAMEDCOM

U.S. Army Medical Command

USAMMDA

U.S. Army Medical Materiel Development Activity

USAMRMC

U.S. Army Medical Research and Materiel Command

USC

United States Code

Section II**Terms****Adverse events**

21 CFR 312.32 defines a serious adverse drug experience as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth

defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. 21 CFR 312.32 also defines unexpected adverse drug experience as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (for example, included in the Investigator Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Approving authority

A military or civilian member of an organizational element of a DA component who has been delegated authority to approve the use of human subjects in research. Per AR 70–25, the approving authority for all greater than minimal risk RDT&E research conducted by DA is the Commander, USAMRMC.

Clinical investigation

An organized inquiry into health problems for all conditions that are of concern in providing health care to beneficiaries of the Military Health Care System, including active duty personnel, dependents, and retired personnel. The Clinical Investigation Program is described in AR 40–38.

Device (as defined in 21 USC 321, Federal Food, Drug, and Cosmetic Act)

The term “device” (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is—

- a. Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;
- b. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or
- c. Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”

Device 510(k)

A 510(k) device is action of the section number of 21 USC 321(h) that allows the FDA to approve a medical device for market if it is substantially equivalent to another medical device already approved. It often requires little or no data to demonstrate substantial equivalence, and it must be reviewed within 90 days.

Drug (as defined in 21 USC 321, Federal Food, Drug, and Cosmetic Act)

The term, “drug” means—

- a. Articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- b. Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- c. Articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- d. Articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D) [21 USCS 343(r)(1)(B) and (r)(3) or (r)(1)(B) and (r)(5)(D)], is made in accordance with the requirements of section 403(r) [21 USCS 343(r)] is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) [21 USCS 343(r)(6)] is not a drug under clause (C) solely because the label or the labeling contains such a statement.”

Human participant in research (from the National Bioethics Advisory Commission (NBAC) Report and Recommendations of the National Bioethics Advisory Commission of August 2001 entitled, “Ethical and Policy Issues in Research Involving Human Participants)

Research should be considered to involve human participants when individuals are— (Excluded from this definition are

deceased individuals, embryos, fetuses, the analysis of non-identifiable data from human beings, and information revealed about others.)

- a. Exposed to manipulations, interventions, observations, or other types of interactions with investigators or
- b. Identifiable through research using biological materials, medical and other records, or databases.

Human subject (as defined in 32 CFR 219.102(f)) (also human participant)

A living individual about whom an investigator conducting research obtained data through intervention or interaction with the individual, or identifiable private information. Intervention includes both physical procedures and manipulations of the subject or the subject's environment for research purposes. The term does not include military or civilian personnel who are qualified to test by assignment to duties that call specifically for such qualifications, such as test pilots and test engineers.

a. A minor (child) is a person who has not attained the legal age for consent to treatments or procedures involved in research under the applicable laws of the jurisdiction in which the research will be conducted.

b. Human subjects may be thought of as direct objects when the research is to determine the effects of a new system on humans (for example, the effect of a vaccine on immunogenicity) or as indirect objects when a test is conducted to determine how humans affect the ultimate performance of a system (doctrine concepts, training programs).

c. Per the NBAC report of 30 April 2001, use of the term, "human participant" is recommended in lieu of the term, "human subject." The term, "human participant" is intended to have the same meaning as human subject as used in 32 CFR 219.102(f).

Human Subjects Research Review Board (as defined by the Office of The Surgeon General)

The principal advisory board of the Commander, USAMRMC for the assessment of practices and procedures by which DA employs human subjects in research, development, testing, and evaluation activities including clinical investigation activities.

Human Use Committee (see AR 70–25)

A committee or board established to provide initial and continuing review of research involving the participation of human subjects. An HUC is an IRB (21 CFR 56), but has somewhat different authority. Within DOD, authority to approve the participation of human subjects in research is vested in commanders. Commanders can approve human subjects research only on the recommendation of duly constituted HUCs. A commander may not approve human subjects research if it is disapproved or deferred by the HUC. Outside the DOD, IRBs are vested with this authority.

Investigational device (as defined in 21 CFR 812.3(g))

A device, including a transitional device, that is the object of an investigation. A transitional device means a device subject to section 520(1) of the FD&C Act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

Institutional Review Board (IRB) (as defined in 21 CFR 56.102)

IRB means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to ensure the protection of the rights and welfare of the human subjects. The IRB should be established, operated, and function in conformance with 21 CFR 56. The term has the same meaning as the phrase "institutional review committee" in section 520(g) of the FD&C Act.

Investigational new drug (as defined in 21 CFR 312.3)

A new drug or biologic used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes. The terms "investigational new drug" and "investigational drug" are deemed to be synonymous.

Investigator (see 21 CFR 312.3 and 21 CFR 812.3)

An individual who actually conducts a clinical investigation; that is, under whose immediate direction the drug is administered or dispensed to a subject or under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Investigator's Brochure

The information to be included in the Investigator's Brochure is found in 21 CFR 312.23(a)(5), "Investigator's Brochure."

IRB of Record (from Food and Drug Administration Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators – “Cooperative Research” and “Non-Local IRB Review”)

The IRB designated with primary responsibility for the oversight and conduct of a particular research protocol to include review of adverse events, protocol amendments, and continuing review of research activities.

Medical Expert

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose. (ICH E6, para 5.3)

New drug (as defined in 21 USC 355. FD&C Act) (p))

The term, “new drug” means—

a. Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a “new drug” if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

b. Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Non-DA sponsored IND

An IND application sponsored by an agency or individual not affiliated with the DA. This definition does not include DA employees who are sponsor-investigators.

Protocol (as defined in the ICH “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance”)

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol-referenced documents. The ORP Web site provides a non-inclusive template for human participant research protocols. Note: All ICH recommendations are not included here. DRAC provides guidance on protocol preparation using FDA-regulated investigational products.

Radiation control committee (see AR 70–25)

A committee appointed by the Commander to ensure that individual users of radioactive materials within the medical facility and each radionuclide used will be approved and controlled. The approval and control must be in accordance with the requirements specified in the conditions of the Nuclear Regulatory Commission license, the DA radioactive material authorization, and appropriate Federal directives.

Research (as defined in 32 CFR 219.102)

A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. Research subject to regulation, and similar terms are intended to encompass those research activities for which a Federal department or agency has specific responsibility for regulating as a research activity, (for example, IND requirements administered by the FDA). It does not include research activities which are incidentally regulated by a Federal department or agency solely as part of the department’s or agency’s broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, wage and hour requirements administered by the Department of Labor).

Research, development, test, and evaluation (as defined in AR 70–25)

The categories of research and development included in Program 6, Research and Development, and operational systems development contained in the Five-Year Defense Program.

Schedule I controlled drug substance

Any drug or substance by whatever official name, common or usual name, chemical name, or brand name listed in 21 CFR 1308.11; DEA Schedule I controlled substances are drugs having a high abuse potential and no accepted medical use (for example, heroin, marijuana, lysergic acid diethylamide).

Sponsor (see 21 CFR 312.3 and 21 CFR 812.3)

A person or other entity that initiates but does not actually conduct a clinical investigation. An entity other than an individual (for example, a pharmaceutical company, governmental agency, academic institution, private organization, or other organization) which uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor, not a sponsor-investigator, and the employees are considered to be investigators. The sponsor of an IDE must be located in the United States (21 CFR 812.18).

Sponsor-investigator (see 21 CFR 312.3)

Sponsor-investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

Subinvestigator (as defined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance”)

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (for example, associates, residents, research fellows). Also see Investigator.

Supplier (of a drug, vaccine, or biological product)

An activity that serves as a provider of drugs, vaccines, and biologicals used in an Army MTF. These providers include commercial pharmaceutical distributors, as well as elements of the military medical logistics system, such as installation medical supply accounts; U. S. Army medical materiel centers; Defense Supply Center, Philadelphia; and medical depots.

Treatment investigative new drug (see 21 CFR 312.34)

The use of a drug that is not approved for marketing, but is under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available, in the treatment of patients not in the clinical trials. The FDA may permit an investigational drug to be used for treatment under a treatment protocol or treatment IND if the drug is intended to treat a serious or immediately life-threatening disease; there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; the drug is under investigation in a controlled clinical trial under an IND in effect for the trial or all clinical trials have been completed; and the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. The “treatment use” of a drug includes the use of a drug for diagnostic purposes.

The Surgeon General-sponsored investigative new drug

An IND application that identifies TSG (or his/her designee) as the sponsor of the application.

Unanticipated adverse device effect (see 21 CFR 812.3)

Unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Section III**Special Abbreviations and Terms**

This section contains no entries.

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