

Investigational Drugs: Investigational Drugs and Biologics

I. PURPOSE

The purpose of this policy is to establish procedures for the proper control, storage, use and handling of investigational drugs and biologics to ensure that adequate safeguards are in place to protect the patient, the staff, the facility and the quality of the study.

II. DEFINITIONS

- A. **Investigational New Drug (IND):** FDA granting of permission that a new drug or biologic may be used in humans prior to FDA review of clinical data that has determined that a particular product is safe and effective for a specific use. Assignment of an IND number or the granting on an IND exemption by the FDA is evidence of such permission.
- B. **Drug:** Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation or prevention of disease or other abnormal condition. Drugs will include biologics as defined below.
- C. **Biologic:** Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of disease or injury.
- D. **Investigational:** A non-FDA approved article or an FDA-approved article used for a non-FDA approved indication, or any other item or placebo permitted by the FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing. This includes those that are already approved by the FDA as safe and effective for specific indications that are being studied for new indications (or doses, strengths, frequency, or uses). Off-label use of an approved drug for therapeutic (non-research) purposes is not considered investigational.
- E. **Investigational Drug:** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. This includes products with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or products used to gain further information about an approved use.
- F. **Administration:** The direct application of a drug to the body of a patient or research subject by injection, inhalation, ingestion or other means.
- G. **Dispense:** To prepare, label, and provide test articles to those who are to use them.

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- H. **Distribution:** Receipt, storage, and dispensing of investigational drug or biologics.
- I. **Emergency Use:** Use of a test article on a human subject in a life-threatening situation where no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.
- J. **Investigational Drug Service (IDS):** A division of the Stanford Hospital and Clinics Department of Pharmacy that provides support for clinical drug studies including Institutional Review Board consultation and dispensing services for investigational drugs or biologics. This division actively supports all Departments and Principal Investigators involved in research.
- K. **Security and Controlled Access Plan:** A plan prepared by the Principal Investigator (PI) that demonstrates adequate control, security and handling of the investigational drugs and biologics including all of the following:
- ensuring the drug or biologic is controlled, used and disposed of in accordance with the IRB approved protocol, any sponsor agreement, applicable FDA regulations (particular 21 CFR 312), applicable Joint Commission requirements, applicable State licensing requirements, and this Policy,
 - administration of the drug or biologic only to participants under the direct personal supervision of the PI or under the supervision of another individual listed on the IRB approved protocol directly responsible to the PI,
 - furnishing of the drug or biologic only to eligible participants under the IRB approved protocol,
 - maintaining accurate, complete and current records (see example of worksheet attached as Exhibit A) of receipt, use or disposition of drugs or biologics, including: (i) the dates of receipt, (ii) dates of dispensing, (iii) quantity currently maintained for dispensing, (iv) name of participant and amount dispensed received, (iv) amounts remaining and method of disposition,
 - providing that if the investigation is terminated, discontinued, or completed, that any unused drugs or biologics are returned to the sponsor or disposed of as directed by the sponsor.

III. POLICY STATEMENT

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It is the policy of SHC and LPCH that investigational drugs and biologics used in human subjects research be stored, handled, and dispensed in full compliance with regulations or requirements of the FDA, JCAHO, California State Board of Pharmacy, other applicable organizations and in accordance with applicable Stanford Hospital and Clinics (SHC), Stanford University Medical Center (SUMC), and Stanford University policies and guidelines. This policy does not cover radiopharmaceuticals.

- A. Distribution of Test Articles (Investigational Drugs or Biologics)
 - 1. It is the responsibility of the Principal Investigator to comply with all Institutional, State and Federal regulations in regards to distribution of investigational drugs and biologics.
 - 2. An Administrative Panel on Human Subjects (IRB) must approve the use of an investigational drug and biologic prior to distribution, except in the case of an Emergency Use.
- B. Investigational Drugs and Biologic Accountability
 - 1. Records of receipt (shipping documents), disposition, destruction and/or return must be kept to document that the investigational drug or biologic has been used according to the protocol.
- C. Storage of Investigational Drugs and Biologics
 - 1. Investigational drugs or biologics used in the context of research may be stored in appropriate areas in another facility other than the Pharmacy under the direct supervision of the Principal Investigator and in accordance with the sponsor, if applicable.
 - 2. Storage facilities for investigational drugs and biologics must be in compliance with Institutional, State, Federal [Food and Drug Administration (FDA)], and Joint Commission on Accreditation of Hospital Organization (Joint Commission) requirements. If the investigational drug or biologic is subject to the Controlled Substances Act, the item will be stored in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure to which access is limited.

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3. Investigational drugs and biologics will be stored under appropriate environmental control in limited access areas separate from routine drug stock. Investigational drugs subject to the Controlled Substances Act for use in inpatients will be stored and distributed by the Stanford Hospital Pharmacy in accordance with the SHC Controlled Substance Policy.

D. Dispensing of Investigational Drugs and Biologics

1. All investigational drugs or biologics administered to inpatients must be dispensed through the Pharmacy, except when the patient brings his or her own investigational drug or biologic to SHC because the patient is enrolled in a study at another institution. In that case, the investigational drug or biologic is governed by SHC's *Patient's Own Medications Policy* and will be administered under that policy by the treating physician(s).
2. If the Pharmacy is not utilized for the dispensing of investigational drugs or biologics, it is the responsibility of the Principal Investigator to assure that dispensing is in accordance with all Institutional, State, Federal, and Joint Commission requirements.
3. Only authorized licensed personnel will dispense and/or administer investigational drugs.
4. Dispensing of investigational drugs and biologics must meet all safety requirements provided by California Pharmacy law for non-investigational drugs.

- E. The Pharmacy will contact the SHC Chief of Staff and/or the Chairman of the P&T Committee in situations where guidance is required in administering this policy.

IV. PROCEDURES

A. Responsibilities of the Principal Investigator

1. The Principal Investigator will provide the Pharmacy with proof of signed Informed Consent (IC) (a copy of the signature page of the IC is acceptable) before the Pharmacy can dispense the investigational drug or biologic.
2. The Principal Investigator will provide the Pharmacy with a copy of

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the FDA Form 1572 or the Protocol Personnel Information as submitted to the IRB listing co-investigators and other study personnel.

3. The Principal Investigator is responsible for placing a copy of the signed IRB-approved IC form in the patient's chart prior to administration of the first dose of the investigational agent or biologic (for inpatients).
4. The Principal Investigator is responsible for the education of co-investigators, study personnel, and SHC personnel who prescribe, distribute, or administer the investigational drug or biologic.
5. The Principal Investigator will work with the Pharmacy regarding the appropriate storage, handling (compounding), and dispensing of investigational drugs and biologics.
6. When receipt or storage or dispensing of investigational drugs or biologics occurs outside of the Pharmacy or its monitoring (e.g., auditing of drugs in outpatient clinics), it is the Principal Investigator's responsibility to: (a) file a satisfactory Security and Controlled Access Plan (see definitions) with the IRB and provide a copy to the Pharmacy, and (b) work with the Pharmacy and IRB to assure that the storage, handling, and dispensing of the investigational drug or biologic is in compliance with such Plan and applicable FDA regulations (particular 21 CFR 812), applicable Joint Commission requirements, applicable State licensing requirements.
7. The Principal Investigator is responsible for working directly with the IDS regarding the costs for the storage, handling (compounding), and dispensing of investigational drugs and biologics. The Principal Investigator and the IDS will work in conjunction to assure adequate funding for these pharmacy costs is incorporated into the grant, contract proposal, or from other internal sources.
8. The Principal Investigator will provide the IDS with a current copy of the protocol, including all revisions or amendments, and the Principal Investigator's Brochure, if applicable, and will keep the IDS informed of any protocol modifications that affect drug therapy or distribution of the investigational drug or biologic.

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9. The Principal Investigator will notify the IDS when the treatment phase of the study has been completed and when the study is terminated.
 10. The Principal Investigator is responsible for the return of unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies.
 11. The Principal Investigator is responsible for reporting all adverse events related to the administration of investigational drugs in accordance with IRB and FDA policy.
- B. Responsibilities of SHC Staff
1. Responsibilities of the Pharmacy
 - a. For each study that drug inventory is managed by the Pharmacy, the Stanford IDS will maintain a protocol specific binder which will be utilized by Pharmacy staff when dispensing the drug or biologic. The binder will contain:
 - (1) Copy of the current protocol
 - (2) The Investigator's Brochure, if applicable
 - (3) Proof of Consent
 - (4) FDA 1572 or IRB Protocol Personnel Information
 - (5) Drug Accountability Records
 - (6) Receipt, Return, Transfer, and Destruction Records
 - (7) Any other information necessary for the Pharmacy to distribute the drug or biologic in accordance with requirements of the sponsor and SHC.

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- b. The Pharmacy will maintain a drug accountability record for each investigational drug stored in the pharmacy. To the extent permitted by the study design, this record shall contain the drug's name, dosage form, strength, lot number and expiration date. This record shall contain dated information regarding the disposition of drug or biologic (amounts received, transferred, wasted, dispensed, returned to sponsor or sent for destruction per SHC Medical Waste Management Program). Names or codes of patients receiving the drug and the name of the Principal Investigator shall be documented and each entry shall be initialed by a Pharmacy staff member.
 - c. Prior to dispensing the first dose of drug, the pharmacist will verify that a signed consent is on file in the Medical Record or that a copy of the signature page is on file in the Pharmacy.
 - d. The Pharmacy will dispense the investigational drug or biologic only on the order of the Principal Investigator or co-investigator as listed on the FDA Form 1572 or the IRB Protocol Personnel Information.
 - e. The Pharmacy will attach a label stating "CAUTION—NEW DRUG LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE" to all investigational drugs and biologics dispensed by the Pharmacy. Prescription labels must contain all information currently required by state and federal laws and SHC policies.

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- f. The Pharmacy will monitor the storage and distribution of investigational drugs stored outside the pharmacy and dispensed in the outpatient clinics (i.e., Stanford Clinics) in accordance with the SHC Pharmacy Medication Storage: Patient Care Area Drug Storage Inspections policy. The pharmacist must ensure that storage, dispensing, accountability, and security comply with federal and state laws and SHC policies. Deficiencies will be documented and reported to the IDS Pharmacist, and corrected appropriately. For PI controlled drugs/biologics outside the Pharmacy, the Pharmacy will issue further guidance on the components of a "Security and Controlled Access Plan" for PI's to use in preparing such a Plan and the IRB to use in reviewing such a Plan. The Pharmacy will also assist and coordinate on the monitoring of PI's compliance with their Security and Controlled Access Plan with the University's Research Compliance Office, which will have the primary responsibility for designing and implementing such monitoring.
- g. Quality Assurance
- (1) Good Clinical Practice guidelines of the International Committee for Harmonization (ICH) will be followed by the Pharmacy when distributing investigational drugs and biologics.
 - (2) Pharmacy dispensing errors or protocol violations, or drug inventory discrepancies will be reported in detail by the IDS pharmacist to the Director of Pharmacy, the sponsor, and the Principal Investigator or study coordinator, along with a description of steps taken to prevent a recurrence.
2. Responsibilities of Authorized Licensed SHC Staff administering an Investigational Drug or Biologic
- a. Verify that a signed informed consent is in the patient's medical record before administering the first dose. If the investigational drug or biologic is from another institution, refer to the "Investigational Drugs or Biologics from Other Institutions" section of this policy and procedure.

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- b. Prior to administering an investigational drug or biologic for the first time, the staff member will demonstrate his/her knowledge of the agent to his/her supervisor or their designee.
- c. Document the administration of the drug or biologic in the patient's medical record.
- d. Document adverse events according to SHC policy and report serious adverse events immediately to the on-call physician or Principal Investigator.

C. Emergency Use of Investigational Drug or Biologic

- 1. The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND. The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.
- 2. The Principal Investigator will notify the Pharmacy of the intent to use the drug or biologic and arrange for shipping of emergency supply of the drug or biologic directly to the Pharmacy along with any pertinent information regarding the pharmacology and preparation of the drug.
- 3. The Principal Investigator will obtain informed consent from the patient or his/her legal representative and place in the patient's medical record.
- 4. If written informed consent is not feasible, the Principal Investigator will obtain the concurrence by an independent physician who is not involved with the clinical investigation and to certify in writing all of the following:

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- a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
 - b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
 - c. Time is not sufficient to obtain consent from the subject's legal representative.
 - d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
5. If, in the Principal Investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical Principal Investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.
 6. The Principal Investigator must notify the IRB within 5 working days after the use of the test article.
 7. The Principal Investigator will provide drug information to the SHC staff treating and monitoring the patient.
 8. FDA regulations allow for one emergency use of a test article without prospective IRB review. The regulations require that any subsequent use of the investigational product at SHC have prospective IRB review and approval.
- D. Investigational Drug or Biologic from another Institution
1. Investigational Drugs from other Institutions will be handled according to the SHC Pharmacy Medication Monitoring: Patient's Own Medication Policy.

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2. The Stanford physician or pharmacist will obtain a summary or copy of the approved investigational protocol which will be placed in the patient's medical record. Another copy will be filed in the Pharmacy.
 3. The Stanford physician or pharmacist will obtain a copy of the informed consent and place it in the medical record. Another copy will be filed in the Pharmacy.
 4. The SHC attending physician or delegate will contact the Principal Investigator to assure that the patient is appropriately followed, and that all relative information is provided regarding the investigational drug or biologic, its effects, contraindications, drug interactions, etc.
- E. Emergency Breaking of Blind in an Investigational Study
1. A mechanism shall be in place to allow pharmacist or other designated health care provider, in a medical emergency during a randomized and blinded trial, to break the blinding code and reveal the identity of the study drug to other health care professionals.

V. RELATED DOCUMENTS

- A. SHC Patient's Own Medications Policy – Pharmacy Policy Manual
- B. SHC Controlled Substances Policy – Pharmacy Policy Manual
- C. SHC Chemical Waste Management Program
- D. SHC Patient Care Drug Storage Area Inspections – Pharmacy Policy Manual

VI. DOCUMENT INFORMATION

- A. Legal Authority/References
 1. Title 22:70263 (O) Investigational Drugs
 2. Joint Commission Comprehensive Accreditation Manual for Hospitals
 3. 21 CFR 312.59; 312.62; 312.61; 312.60; 312.69; 50:23a;
 4. California State Board of Pharmacy Law
 5. Guideline for Industry E6 Good Clinical Practice: Consolidated Guidance
- B. Author/Original Date

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- C. Gatekeeper of Original Document
Administrative Manual Coordinators and Editors
- D. Distribution and Training Requirements
 - 1. This policy resides in the Pharmacy Manual of Stanford Hospital and Clinics.
- E. Review and Renewal Requirements
This policy will be reviewed and/or revised every three years or as required by change of law or practice.
- F. Review and Revision History
May 1991, R. Miller, Director of Pharmacy
February 1994, S. White, Director of Pharmacy
August 1995, to reflect Stanford Health Services title
February 1997, S. White, Director of Pharmacy
August 1997, S. White, Director of Pharmacy
April 2000, S. White, Director of Pharmacy
September 2003, M. Hamilton, IDS Pharmacist
August 2005, M. Hamilton, IDS Pharmacist
February 2006, M. Hamilton, IDS Pharmacist
June 2009, M. Hamilton, IDS Pharmacist, K. Lucas Medication Safety Pharmacist
- G. Approvals
December 2003, SHC Medical Board
December 2003, SHC Board of Directors
August 2005, SHC Pharmacy and Therapeutics Committee
September 2005, SHC Quality Improvement and Patient Safety Committee
October 2005, SHC Medical Board
November 2005, SHC Board of Directors
August 2006, SHC Medical Board
August 2006, SHC Board of Directors
June 2009, P&T Committee