1 PURPOSE

1.1 To establish guidance for the receipt, storage, handling, dispensing, accountability, returns and destruction (wasting) of investigational drugs and biologics used in Sharp HealthCare (SHC) Institutional Review Board (IRB) approved clinical trials protocols. The terms “investigational drug” and “drug” are deemed to be synonymous for the purpose of this Guidance.

1.2 The guidance begins when an investigational drug is received at a SHC facility, or when a lawfully marketed drug for the indication under study from a SHC facility has initiated active drug treatment in a prospective drug study.

1.3 The guidance ends when the drug(s) being studied have met their final disposition, which is either destroyed on site, returned to sponsor, or transferred to a different study or site.

1.4 This guidance is to be reviewed and updated annually, or more often as needed, by the primary Investigational Research Pharmacists who manage the investigational drugs.

2 REVISIONS FROM PREVIOUS VERSION

2.1 If applicable, previous versions available in Human Research Protection Program Change Log.

3 POLICY STATEMENT

3.1 Per SHC POLICY: Investigational Drugs and Biologics (43019.01)

4 RESPONSIBILITIES

4.1 Principal Investigators (PIs), Sub investigators, Clinical Research Coordinators (CRCs), Investigator-Sponsors, Pharmacists, and Sponsor’s Study Monitors/Auditors carry out these procedures.

5 PROCEDURE

5.1 Drug Receipt, Storage and Documentation: Each clinical trial is to have designated site and/or pharmacy personnel manage investigational drugs. Those designated personnel are listed on the Protocol-Specific Site Delegation Log and the Protocol-Specific Site Training Log prior to executing any pharmacy protocol required functions; exceptions may apply in emergency situations. A Site Delegation Log and Site Training Log are to be maintained in the PI/research site regulatory binder.

5.2 Pharmacy Binder: If not provided by the Sponsor, the investigational pharmacy personnel are responsible for creating a clinical trial protocol-specific pharmacy binder or electronic file which will contain the following:

5.2.1 Patient Enrollment List: A master list is maintained for documenting patients enrolled in the clinical trial along with assigned patient number and/or randomization number. *WORKSHEET: Pharmacy Patient Enrollment (HRP-326)* may be used as a guide.

5.2.2 Investigational Drug Summary: *WORKSHEET: Investigational Drug Summary (HRP-351)* may be used as a guide.

5.2.3 Pharmacy Manual, if provided by the Sponsor.

5.2.4 Drug Accountability Forms: The investigational pharmacists may use sponsor-provided or SHC-created drug accountability forms (*WORKSHEET: Master Drug Accountability Record [IV Meds] [HRP-327]* and *WORKSHEET: Master Drug Accountability [Oral Drugs] [HRP-328]*).

5.2.4.1 At the completion of the study, a copy of the Drug Accountability Form is to be maintained in the protocol-specific pharmacy binder. To the extent permitted by the study design, this Drug Accountability Form may contain the drug’s name, dosage form, strength, lot/batch number, and expiration date where applicable.

5.2.4.2 The Drug Accountability Form may contain dated information regarding the disposition of drug (amounts received, transferred, wasted, dispensed, returned to sponsor, sent for destruction, or destroyed on site) per *POLICY: Pharmaceutical Waste Management (18306.99)*.

5.2.4.3 When a lawfully marketed drug from existing stock at a SHC facility is being used in a prospective clinical investigation, documentation of its receipt at the facility from the vendor is not required on the Drug Accountability Form.

However, the specific information about the drug that was dispensed is documented in the pharmacy binder.

5.2.5 Study Protocol and Amendments: The protocol-specific pharmacy binder is to contain the most recent version of the clinical trial protocol. Previous versions of the protocol and all amendments will be retrievable from the investigator/research site's regulatory binder. An electronic version of the current version of the protocol may also be kept on file in the pharmacy database with an insert in the pharmacy binder identifying its location.

5.2.6 Investigator's Brochure (IB) and Amendments: The protocol-specific pharmacy binder is to contain the most recent version of the investigator brochure. Previous versions of the investigator's brochure (IB) and all amendments will be retrievable from the investigator/research site's regulatory binder. An electronic version of the current investigator brochure may also be kept on file in the pharmacy database with an insert in the binder identifying its location.

5.2.7 Patient Data: All patient specific dispensing information is to be retained in the pharmacy binder. Items will be study specific and may include investigational drug orders, completed transport logs, randomization, and drug assignment confirmations (if applicable), and verification of informed consent.

5.2.8 Shipping and Receiving Invoices: All shipping and receiving invoices are to be retained in the protocol-specific pharmacy binder.

5.3 Correspondence: Documentation of all correspondence pertaining to the study will be retained in the protocol-specific pharmacy binder.

5.4 Receipt of Investigational Drug: Upon receipt of the investigational drug from the sponsor (e.g., pharmaceutical company), the investigational drug is to be logged onto the Drug Accountability Forms in accordance with protocol guidelines and Section 5.2.4 above.

5.5 Storage of Investigational Drug: Investigational drug is to be stored in a locked research storage area or cabinet within the pharmacy that is separate from non-investigational drugs. Storage and handling of lawfully marketed drugs supplied from a SHC facility for clinical trials will be described in the protocol-specific pharmacy binder.

5.5.1 When the investigational drug is in the custody of the pharmacy, the pharmacy is to keep temperature logs and monitor on a daily or continual basis to ensure the investigational drug remains within the specified temperature ranges. *WORKSHEET: Investigational Pharmacy Temperature Log (HRP-323)* can be used as a guide for those sites logging the temperature once per day.

5.5.2 Temperature logs are for use with multiple investigational drugs and are not kept in the protocol-specific pharmacy binder unless the sponsor requires copies to be maintained in the protocol-specific pharmacy binder. Temperature logs are made available to sponsor monitors and auditors upon request.

5.6 Storage of Investigational Drug at a Non-SHC Facility: If an investigational drug is stored at a facility other than a SHC pharmacy but is to be dispensed through the SHC pharmacy, it is to be transported by designated research site staff and delivered to designated SHC pharmacy staff under the continuous control of the designated site study staff. When transporting investigational drug to or from another facility follow procedures outlined in Section 5.18 below.

5.7 Excursions: If the investigational drug goes outside of the sponsor-specified temperature range during transport or storage it is called a temperature excursion. The excursion is reported to the study sponsor and the drug is retained in quarantine. The pharmacy is to follow the protocol-specific procedures regarding reporting temperature excursions.

5.7.1 If follow-up documentation from the sponsor supports the drug is viable for use in the clinical investigation after the reported temperature excursion, then the drug may be removed from quarantine and designated as usable stock.

5.7.2 If the sponsor deems the drug as unusable, the drug will be quarantined until final disposition can be determined.

5.7.3 For investigator-initiated studies involving marketed drugs without sponsor-specified temperature ranges, the manufacturer's labelled storage temperature requirements shall be used, and the manufacturer should be contacted to determine their recommended acceptable temperature excursion parameters. These parameters should then be included in the protocol-specific pharmacy binder.

5.8 Ordering and Dispensing for SHC Approved Studies:

5.8.1 The investigator or designee is responsible for providing the pharmacy with a method of confirming a patient or legally authorized representative (*GUIDANCE: Legally Authorized Representatives (Surrogate Consent) [HRP-013]*) has consented to participate, according to study-specific Sharp IRB approved consent requirements, prior to dispensing the first dose of the investigational drug.

5.8.2 Investigational Drug Orders: The SHC treating physician, investigator, or designee shall write or electronically enter orders that include identification of the drug, dose, route, frequency, and administration instructions to be followed by the nursing staff, unless this information is blinded as part of the study protocol. For drug orders that are not entered into the Electronic Medical Record (EMR) for outpatient use, the written orders are to contain all the essential elements of a drug order as required by law.

5.8.3 Order Verification: For drug orders entered into the EMR, the pharmacist will verify the order. If not already included in the EMR, the pharmacist should add necessary comments indicating that the medication is an investigational drug and other information/instructions for drug administration, drug stability, etc.

5.8.4 In studies that have an interactive voice response system (IVRS/ IWRS) to assign drug/placebo, the sponsor will define responsibilities for IVRS/ IWRS within the study protocol. The pharmacy will dispense the drug in accordance with allocation information.

5.8.5 For subjects who are enrolled in drug studies while admitted in a Sharp hospital (inpatient studies), the pharmacy will dispense based on site routine standard of practice in accordance with local laws and regulations.

5.8.6 Patients enrolled in outpatient clinical trials approved by SHC who are admitted to a SHC hospital may continue taking an investigational drug provided the admitting physician orders the study drug. The SHC treating physician or designee is responsible for contacting the study principal investigator, CRC, or designee to assess the appropriateness of continuing the investigational drug (including its effects, contraindications, drug interactions, etc.) during the hospitalization.

5.8.7 For subjects admitted to the hospital who are actively enrolled in a study prior to admission (outpatient studies) for SHC and non-SHC studies, the investigational drug must be provided by the patient or family in the original container/package provided by the study site. Investigational drugs are to remain in their original packaging at all times in the pharmacy. As with inpatient studies, each dose will be dispensed prior to the administration time. The *"Patients Own Medication" procedure (Policy # 43088.99)* must be followed. Upon discharge, the patient's investigational drug will be returned to the patient or the patient's family/ representative in the original container.

5.8.8 Any investigational drug that is a controlled substance must be inventoried and stored in its original packaging in a secure fashion and accounted for. If the bottle/ package cannot be loaded into an individual Pyxis pocket for such purposes, it will be handled on a case-by-case basis.

5.9 Protocol-Specific Investigational Drug Education: For SHC approved studies, the sponsor is responsible for providing protocol-specific investigational drug education to the PI, sub-investigators, CRCs, research site personnel, and SHC pharmacy personnel who prescribe, store, dispense, or administer the investigational drug.

5.10 Updated Information and Documents: The CRC or designee is responsible for providing the pharmacy with a current copy of the protocol, including all revisions or amendments, a current

copy of the Investigational Brochure (IB), and keeps the pharmacy informed of any new information that may affect patient safety or dispensing of the investigational drug.

5.11 Investigational Drug Disposition: The CRC and/or the SHC pharmacist keeps adequate records of the disposition of the investigational drug/biologic, including dates and quantities of dispensing, quantity currently maintained for dispensing, quantities and dates of quarantined stock and quantity and dates of drug units that have been destroyed on-site or returned to the Sponsor.

5.12 Accountability, Returns, and Destruction: The CRC and/or pharmacist maintain all drug accountability logs and accounts for all investigational drug dispensed, unused, used, and expired. If investigational drug and/or packaging are not returned by subjects who are outpatients, the CRC is to make all efforts to retrieve the package and/or investigational drug, including sending certified letters requesting the return of investigational drug to subjects who are lost to follow-up.

5.12.1 At study completion, sponsor-supplied Food and Drug Administration (FDA) approved investigational drugs or products are to be returned to the sponsor or destroyed on site. With sponsor approval, the sponsor-supplied FDA approved investigational drug or product may be transferred to another IRB approved study. Sponsor provided investigational drugs or products are not used outside of a clinical trial.

5.12.2 Non-FDA approved investigational drugs or products are to be returned to the sponsor or destroyed on site. With sponsor approval or direction, the sponsor-supplied non-FDA approved investigational drug or product may be transferred to another IRB approved study.

5.12.3 For all COVID-19 studies, any drug that is dispensed to a designated COVID-19 unit is not to be returned to the pharmacy. After conducting a drug count on the floor, completing final disposition documentation, and sharing the disposition document with the pharmacy, the drug is to be destroyed in accordance with facility pharmaceutical waste management practices (*POLICY: Pharmaceutical Waste Management [18306.99]*).

5.12.3.1 Study patients who have or contract COVID during their study participation may not be required to return their study medications to the investigational pharmacy.

5.12.3.2 In recognition that COVID-19 safety precautions may be revised over time, pharmacists and CRCs will follow the current practices that are in place at the SHC site.

5.13 Clinical Trial Treatment Phase Termination: The principal investigator or designee notifies the pharmacy when the treatment phase of the clinical trial has been completed and when the study is terminated.

5.14 Sponsor Monitors and Auditors: The sponsor or their designee is to routinely monitor (audit) all clinical trials. The sponsor's monitor manages investigational drug returns or oversees wasting (destruction) according to sponsor protocol and/or SHC procedures *(POLICY: Pharmaceutical Waste Management [18306.99])*.

5.15 Investigational Drug Wasting for IND Studies:

5.15.1 The pharmacy is to log all returns, wasting, and the drug's final disposition as outlined in 5.2.4.

5.15.2 For all oral containers and non-chemotherapy injectable containers, the designated monitor is instructed to verify each drug container to be destroyed on-site or to be returned to the Sponsor with the delegated Research Pharmacy team member. The monitor is to communicate the approval for the final drug disposition with the Pharmacy.

5.15.3 Chemotherapy injectable containers that are used for compounding are to be placed in the designated chemotherapy waste container located in the IV room immediately after sterile compounding and not saved for monitor verification to reduce the risk of occupational exposure recommended by USP-800.

5.16 Investigational Drug Wasting for Investigator Initiated Studies/Non-routinely monitored studies:

5.16.1 Individuals overseeing investigational drug dispensing and/or administration must determine if the study meets criteria for being an investigational drug study, and if so, document all returns, wasting, and the drug's final disposition as outlined in 5.2.4, using the *WORKSHEET: Master Accountability Record (HRP-327 or HRP-328)* or as specified by the protocol and/or study specific investigational drug handling instructions.

5.16.2 If it has been determined that the study does not meet criteria for being an investigational drug study, individuals overseeing investigational drug dispensing and/or administration will manage wasting (destruction) according to the protocol and/or SHC procedures (*POLICY: Pharmaceutical Waste Management [18306.99*]).

5.17 Controlled Substances Act: If the investigational drug is subject to the Controlled Substances Act, the pharmacist, principal investigator, sub-investigators, and CRC are to take adequate precautions to prevent theft or diversion of the substance into illegal channels of distribution.

5.18 Inter-facility Investigational Drug Transport: When an investigational drug is transported by courier or SHC staff member to a different site or entity before or after drug preparation, it is to be accompanied by a transport log that captures what is being transported, the time/date of transportation, who is transporting the container(s), the time/date of the receipt and who is receiving the container, at a minimum.

5.19 Other information may be on the transport log dependent upon the specific requirements of the study. An example of a transport log is *WORKSHEET: Investigational Drug Transport Log (HRP-325)*: This document is also termed "Chain of Custody" documentation that may be supplied by the sponsor. The sponsor may require additional information regarding chain of custody that is not specified above.

5.20 If *WORKSHEET: Investigational Drug Transport Log (HRP-325)* is used, the following are instructions for use:

5.20.1 The pharmacist or designee completes the information in the header and Investigational Drug Dispensation section of the Transport Log.

5.20.2 A copy of the partially completed Transport Log is kept at the pharmacy and held until the pharmacy receives a faxed or scanned copy of the completed Transport Log. The clinical research coordinator is to keep the original completed Transport Log in the protocol- specific binders at the research site.

5.20.3 Courier staff or the CRC completes the Transport section of the Transport Log.

5.20.4 Investigational Drugs requiring refrigeration during transport from the Sharp Memorial Investigational Pharmacy to the Grossmont Cancer Center or the Chula Vista Cancer Center will use an insulated cooler bag with a temperature monitoring device attached to each investigational drug unless otherwise specified by the sponsor.

5.20.5 The temperature monitoring device is to be started at the time of preparation and placed on top of the investigational drug, which is then wrapped with gel-packs.

5.20.6 The courier or CRC signs the Investigational Drug Transport Log at the time of pick-up.

5.20.7 The SHC staff receiving the drug stops the temperature monitoring device and completes the information in the Transport Site section of the Investigational Transport Log.

5.20.8 If there is an alarm/alert indicating that the temperature in the drug transport cooler bag went outside of the protocol defined ranges (excursion), the pharmacist and CRC are to be informed immediately and the drug is not to be administered to the patient until the dispensing pharmacist analyzes all alarm/alert data from the temperature monitoring device and communicates the excursion information to the protocol sponsor.

5.20.9 The sponsor's medical monitor or designee reviews the temperature excursion data and determines if the drug is suitable for administration. If the drug is deemed not suitable for administration, the study coordinator coordinates with the pharmacy and patient for scheduling the next available investigational drug administration.

5.20.10 If the sponsor's medical monitor or designee determines that the study drug was not compromised by the temperature excursion and is appropriate for administration, the research pharmacist contacts the study coordinator to release the drug for use. The sponsor is to provide written documentation that the drug is suitable for use.

This documentation is to be stored in the protocol specific pharmacy binder with a copy stored in the research site's regulatory binder.

5.20.11 Unless the sponsor specifies differently, oral drugs that do not require refrigeration during transport will not include a temperature monitoring device. However, the Investigational Drug Transport Log is to be used by the courier or CRC at pick up. SHC staff are to document receipt to retain the chain of custody and account for appropriate drug transfer.

5.21 Emergency Use of Investigational Drug: In the event of a one-time emergency use of an investigational device, drug, or biological product in a life-threatening situation physicians/ investigators are to follow guidelines according to the *GUIDANCE: Emergency Use Review (HRP-023)*. FDA regulations allow for one emergency use of an IND without prospective IRB review. Any subsequent use of the IND shall undergo prospective IRB review and approval.

5.22 Emergency Breaking of a Blinded Investigational Drug in a Clinical Trial: A study-specific mechanism shall be in place to allow a 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 investigational drug to other health care professionals as needed for the medical care of the patient. The sponsor is to provide the instructions for breaking the blind before any investigational drug is dispensed.

5.23 Investigational Drug Adverse Reaction Reporting: The principal investigator, CRC, or designee is to report adverse drug events according to the FDA and sponsor's requirements. Investigators or their designees report certain adverse events directly to the IRB using *FORM: Promptly Reportable Information (HRP-214)*. The SHC staff documents adverse events according to *POLICY: Medication Safety Event Monitoring (48138.99).* Refer to *the MANUAL: Investigator Guidance Manual (HRP-101)* for guidance on submission of a report on adverse events and other promptly reportable information.

5.24 Record Storage: Store dispensing records for closed studies in a secure area that is readily retrievable until two years after the investigational drug receives FDA approval or until the sponsor notifies the investigator that investigational drug records are no longer needed. The sponsor or investigator may request that the dispensing records for closed studies be filed with the investigator's regulatory binders.

5.25 Billing for Investigational Drug Dispensing and Drug Charges: The pharmacist, pharmacy technician or their designee is responsible for entering agreed upon charges into the SHC billing system within two months of the dispensing. This includes charges for all activities associated with investigational drug dispensing and protocol-required FDA approved medications not provided by the study sponsors.

5.26 Annual Review of *GUIDANCE and POLICY: Investigational Drugs.* This guidance and *POLICY: Investigational Drugs (43019.01)* are to be reviewed and updated (as needed) by October 1st each year by all SHC investigational drug pharmacists involved with managing investigational drugs or biologics. SHC primary investigational drug pharmacists are to acknowledge annual review of the POLICY and this guidance by signing *WORKSHEET: Annual Investigational Drug Policy and Guidance Review Log (HRP-329)*.

6 MATERIALS

6.1 POLICY: Investigational Drugs and Biologics (43019.01)
6.2 POLICY: Patient's Own Medication (43088.99)
6.3 POLICY: Medication Safety Event Monitoring (48138.99)
6.4 POLICY: Pharmaceutical Waste Management (18306.99)
6.5 GUIDANCE: Legally Authorized Representative (Surrogate Consent) (HRP-013)
6.6 GUIDANCE: Emergency Use Review (HRP-023)
6.7 MANUAL: Investigator Guidance (HRP-101)
6.8 FORM: Promptly Reportable Information (HRP-214)
6.9 WORKSHEET: Investigational Pharmacy Ambient Temperature Log (HRP-323a)
6.10 WORKSHEET: Investigational Pharmacy Refrigerator Temperature Log (HRP-323b)

7 REFERENCES

7.1 (21 CFR 321.32(b))
7.2 21 CFR 312
7.3 21 CFR 601

This document is available on www.sharp.com/research, IRBANA or by contacting research@sharp.com.