Title: Core Standard Operating Procedure for the Handling of Investigational Pharmaceutical Products

I. Procedure Statement
To describe the procedures for managing investigational products in clinical trials, including receipt, storage, dispensing, administration, and accountability after approval of the product has been secured by MU Health.

II. Definitions
1. Biologic: A product such as a vaccine, blood and blood component, allergenic, somatic cell, gene therapy, tissue, and recombinant therapeutic protein.

2. Combination Product: Includes: (1) a product comprised of two or more regulated components, such as a drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed, and produced as a single product; (2) two or more separate products packaged together in a single package or as a unit, and comprised of drug and device products, device and biological products, or biological and drug products; (3) a drug or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved specified drug, device, or biological product, where both are required to achieve the intended use, indication, or effect, and where upon approval of the proposed product the labeling of the approved product would need to be changed (for example, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); and (4) any investigational drug or biological product packaged separately that according to its proposed labeling is for use only with another specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

3. Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

4. Investigational New Drug Application (IND): A request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

III. Procedure/Content/Scope
This SOP will apply to all clinical trials research within MU Health including the School of Medicine, School of Health Professions, School of Nursing, and MU Healthcare. This SOP will cover the processes and procedures to follow with respect to investigational products (IP) including drugs, biologics, vaccines, and combination products. The Investigational Drug Service
(IDS) pharmacist and principal investigator (PI) should ensure that the IP is used only in accordance with the approved protocol. Depending on the respective sponsor’s policy, an IP may include study-specific concurrent medication and treatment such as the comparator drug or placebo and rescue medication. The IDS pharmacist is available Monday to Friday from 8:00 am to 4:30 pm. Outside of these hours, the inpatient pharmacist can assist with the dispensing of IP.

1. **Initial Setup and Assigned Duties and Responsibilities:**
   a. Prior to the start of the study, the PI should ensure that appropriate FDA notification, approval, and clearance of the IP have been received for the applicable study activity.
   b. The PI or research staff should send the IDS pharmacist a copy of the protocol and investigator’s brochure (or package insert for approved drugs). The PI or research staff and IDS pharmacist should work together to create a fee schedule for all IP.
   c. The study sponsor must be informed that all IPs are to be shipped directly to the IDS pharmacy, unless stated otherwise in the protocol.
   d. The PI or research staff is to provide advance notice to the IDS pharmacist regarding research subject dispensing visits/needs, sponsor/funding agency monitoring visits, and closeout visits/activities.
   e. The PI is to ensure that the study prescription or inpatient order is clear and complete.
   f. The PI delegates to the IDS Pharmacy responsibility for the receipt, dispensing, accountability, and record keeping for all research medications used in human research studies. The PI, however, retains ultimate responsibility for IP management, use, and accountability.
   g. The IDS pharmacy complies with all federal, state, and institutional regulations for labeling, storing, dispensing, and accounting of medications used in clinical research. It also complies with procedures outlined in the study protocol.

2. **Receipt of IP:** The IDS pharmacist should do the following:
   a. Perform a final check on the required IP storage conditions to ensure the IP can be stored as per requirements set forth by the sponsor or as designated by the protocol.
   b. Once the IP is delivered, check for any inconsistencies in the appearance of the IP and/or its container, the environment that the IP is stored in upon delivery, if necessary, and the total quantity of the IP that has been delivered.
   c. Upon delivery of the IP, sign the receipt slip or delivery notice. If necessary per protocol, send confirmation to the sponsor or CRO.
   d. File all shipping records, signed receipt slips or delivery notices in the pharmacy site file.
   e. Update the quantity of IP on the electronic drug accountability log currently in use by the IDS pharmacy.
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3. **Storage of IP:** The IDS pharmacist should do the following:
   a. Ensure that the IP is stored immediately according to the conditions stated in the protocol and that the location is secure and limited to research personnel.
   b. Ensure that the storage premises are in an area designated for IP only and that the IP will not be stored with non-clinical trial medications or biologics. The premises should be secured with limited access.
   c. Record the storage temperature, if applicable, once every working day on a temperature log.
   d. Ensure that the randomization code has been received and properly documented, if applicable.
   e. Store expired or unused IP for a maximum of 6 months. If the sponsor is unable to accept returns during that period, the IDS pharmacist will dispose of the IP per IDS SOP.
   f. Store unused IP in a secure location, separate from active inventory.
   g. When discrepancies or violations of the storage condition are detected, report such problems to the sponsor or CRO.

4. **Dispensing and administration of IP:** The IDS pharmacist, PI, or research staff, as appropriate, should do the following:
   a. Review sponsor or CRO provided SOPs or procedures regarding protocol requirements for dispensing and administering IP.
   b. Limit dispensing of IP to a licensed pharmacist, physician, dentist, or other approved licensed provider. Research staff will retrieve IP from the IDS as necessary for study visits following appropriate documentation (log) and procedures for IP removal and transport to research area.
   c. Follow protocol requirements regarding IP and medication administration. When the protocol specifically allows, abide by hospital-specific procedures for medication administration.
   d. For randomized studies, follow the study randomization procedures in allocating the assigned IP to the study subject.
   e. Check the expiration date prior to use or dispensation of the IP.
   f. Follow sponsor and protocol-defined procedures to track identifiers for the IP in blinded studies. Ensure that each subject receives the correct IP, and document the expiration date.
   g. For open-label studies, dispense the correct IP in the correct dosage to each subject and document the expiration date.
   h. When administering intravenous IP, arrange for proper facility location and room ahead of time.
   i. For self-administered IP, provide instructions to the subject on how to use and store the IP.
   j. Instruct subjects on how to complete a medication diary, if applicable.
   k. In the event that a research subject misses an appointment, the IP must be returned to the IDS pharmacy immediately.
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I. Instruct the subject to return any unused IP at the next study visit or in accordance with the protocol.

m. Count and document unused IP that is returned by the subject.

n. Document all IP dispensed, administered, and returned on the electronic drug accountability log, including, but not limited to:
   i. Subject and IP identifier.
   ii. Batch or lot number.
   iii. Date of IP preparation.
   iv. Expiration dates, if known.
   v. Quantities dispensed or administered, returned or destroyed.
   vi. Initials or signature of the qualified study personnel member who performed the specific activity.
   vii. When giving intravenous IP, administration start and completion times should be documented on study-specific source documents, as appropriate.

o. Report to the sponsor any IP discrepancies, abnormalities or defects.

p. Follow MU’s unanticipated problems procedure for adverse events and protocol deviations related to IP.

5. Request for IP resupply: The IDS pharmacist should do the following:
   a. Routinely monitor products that are not automatically resupplied for adequate availability of on-site IP.
   b. Ensure expiration dates are noted and monitored on a regular basis.
   c. When more supplies are needed, make a request to the sponsor per their resupply instructions.
   d. After resupply arrives, follow receipt of IP procedures outlined above.

6. Return and Reconciliation of IP: The IDS pharmacist and PI or research staff, as appropriate, should do the following:
   a. Ensure that the reconciliation procedure has been discussed and agreed upon with the sponsor.
   b. Ensure that the study monitor has checked the accountability log before reconciliation of the IP.
   c. Follow the protocol/sponsor requirements for returning the IP to the sponsor, or for local destruction of IP, if specified in the protocol.
   d. For return of IP to the sponsor, document the following on the reconciliation log:
      i. Description of what was returned.
      ii. Quantity of returned IP.
      iii. Date of transfer of the IP to the sponsors designated personnel, as applicable.
      iv. Date and initials or signature of qualified study personnel coordinating the transfer.
      v. Keep and file shipping documentation, as applicable.
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e. For disposal or destruction of IP locally, document the following on the reconciliation log:
   i. Specific IP disposed or destroyed.
   ii. Quantity disposed of or destroyed.
   iii. Date of transfer of the IP to the disposal or destruction company.
   iv. Date and initials or signature of the qualified study personnel coordinating the disposal, destruction, or transfer of the IP.

f. The IDS pharmacist may liaise with the sponsor to arrange for the retrieval of used IP by the study monitor, or the local destruction of the IP six months after use or expiration per IDS SOP.

g. The reconciliation log should be regularly maintained and updated in the pharmacy site file.

IV. References:

1. MU Health policies related to Investigational Device Exemptions and VAT.


3. FDA Combination Product Definition: http://www.fda.gov/combinationproducts/aboutcombinationproducts/ucm118332.htm
