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SOP 8.01 – FDA Regulated Drugs and Biologics

1. Objective

This SOP discusses considerations for clinical investigations that involve the use of drugs, biologics as discussed in federal regulations 21 CFR 312, 21 CFR 50, 21 CFR 56.

2. General Description

Definitions

Clinical investigation - any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.

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

IND - is an investigational new drug application. "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Test Article - A test article is any drug, biological product, or medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act. (21 CFR 56.102(1))

Biological Product - Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other technologies.

Emergency Use - Emergency use is defined as the use of a test article with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d))

Physician-investigator - A licensed physician who administers an investigational drug for an expanded access use is considered an investigator (i.e., physician-investigator) and must comply with the responsibilities for investigators. Physician-investigators must maintain and retain accurate records that include a case history of the patient and the disposition of the drug as required.

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3. Roles & Responsibilities

Execution of SOP: Principal Investigators (PI)/Study Personnel (SP), IRB Chair, IRB, Office of Research Integrity – Human Subjects (ORI-HS) Staff

PIs

In conducting clinical investigations of drugs, including biological products regulated under 21 CFR 312, the PI is responsible for:

- Protecting the rights, safety, and welfare of subjects;
- Ensuring that the clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, the investigational plan/protocol, and applicable regulations;
- Controlling the drug(s), and/or biological product(s) under investigation including storage, security, dispensing, administration, return, disposition and records of accountability. This responsibility may necessarily need to be shared with other entities or groups, such as a pharmacy;
- The investigator is responsible for reporting all unexpected adverse events to the FDA within 10 working days;
- All adverse events that require prompt reporting to the IRB are to be reported according to IRB policies and procedures (See SOP 11.01 Problems and Adverse Events, Record and Report);
- The PI is responsible for notifying the sponsor of adverse events as specified in the protocol;
- Maintaining current records for all research team members documenting valid licenses.

Additional responsibilities may include, but are not limited to:

- Providing reasonable medical care to study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention;
- Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual.

Sponsors, Sponsor-Investigators re Expanded Access IND (21 CFR 312, Subpart I)

An individual or entity that submits an expanded access IND or protocol under 21 CFR 33 Subpart I is considered a *sponsor* and must comply with the responsibilities for sponsors. A licensed physician who submits an IND for expanded access use under 21 CFR 33 Subpart I is considered a *sponsor-investigator* and must comply with the responsibilities for sponsors and investigators. In accordance with 21 CFR 33, Subpart D, Investigator-sponsors must ensure physician-investigators:

- are qualified to administer the investigational drug for the expanded access use;
- provide the physician-investigator with the information needed to minimize risk and maximize the potential benefits of the investigational drug (e.g., Investigator's Brochure);
- maintain an effective IND for the expanded access use;
- maintain and retain adequate drug disposition records in accordance with FDA and institutional requirements; and
- comply with FDA requirements for submission of IND safety and annual reports.

IRB

The IRB will review clinical investigation proposals in accordance with 21 CFR 312, 50 and 56 where applicable. The following categories of clinical investigations are not regulated by DHHS or another federal agency and are exempt from the requirements of FDA regulations for IRB review:

- Emergency Use of a Test Article

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21 CFR 56.104(c) - Emergency use of a test article is exempt from prior IRB review and approval, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. **Important note:** At this time, UNLV does not actively conduct or manage planned emergency research; as such, UNLV does not have policies in place for such research. PIs interested in conducting planned emergency research must contact ORI-HS to discuss the possibility of engaging in this type of research.

- Taste and Food Quality Evaluations and Consumer Acceptance Studies
21 CFR 56.104(d) - Studies where wholesome foods without additives are consumed or a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

4. Procedures

Investigational New Drug (IND) Requirements

When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, an IND may be required. General requirements and considerations toward obtaining an IND are discussed under 21 CFR 312.

Investigators are asked on the IRB protocol proposal form to indicate whether the research involves drugs. If so, they will be asked if there is an IND for the research. If there is, they will be asked for evidence of the IND, which may include:

- industry sponsored protocol with IND,
- letter from FDA,
- letter from industry sponsor,
- other document and/or communication verifying the IND

When research is conducted to determine the safety or effectiveness of a drug the IRB will review the application based upon the documentation provided and determine:

- that there is an approved IND in place, or
- that the FDA has determined that an IND is not required.

If the research involves drugs and there is no IND, the Principal Investigator must provide a rationale why it is not required.

An IND may not be necessary if the following conditions are met:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug (FDA will not accept an application for an investigation that is exempt under this provision);
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- 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;
- the research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50 respectively), and does not intend to invoke 21 CFR 50.24, exception from informed consent requirements for emergency research, and

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- The investigation is conducted in compliance with the requirements of 312.7.

In addition to the above, these conditions may also be applicable toward exemption for IND requirements:

- A clinical investigation involving one or more of the following in vitro diagnostic biological products: blood grouping serum; reagent red blood cells; and anti-human globulin is exempt if:
 - it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure, and
 - it is shipped in compliance with 312.160.
- A drug intended solely for tests in vitro or in laboratory research animals is exempt if shipped in accordance with 312.160.
- A clinical investigation involving use of a placebo is exempt if the investigation does not otherwise require submission of an IND.

Note: An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

The IRB cannot grant approval to the research until the IND status is determined, and, if necessary, an approved IND is in place.

Investigator-Sponsors

In reviewing research involving FDA regulated articles, the IRB determines if the study involves an investigator-sponsor. If so, the IRB informs the investigator that there are sponsor responsibilities, including reporting requirements to the FDA, (as well as the investigator responsibilities) and all these requirements are his/her responsibility.

Open Label Protocol or Open Protocol IND

When a controlled trial has ended, treatment may be continued to allow participants to continue to receive the benefits of the investigational drug until marketing approval is obtained. These are considered uncontrolled studies that are carried out to obtain additional safety data (Phase 3 studies).

Expanded Access (Treatment) Uses of Investigational Drugs

FDA regulations, 21 CFR 312.300 - 320, describe the requirements for the use of investigational and approved drugs where availability is limited by a risk evaluation and mitigation strategy when the primary purpose of the use is to diagnose, monitor, or treat a patient's disease or condition (i.e., expanded access uses). By authorizing such expanded access uses, FDA aims to facilitate the availability of such drugs to patients with serious or life-threatening diseases or conditions when there is no comparable or satisfactory alternative therapy.

The following requirements apply to FDA and IRB determinations for expanded access uses, whether under a new IND or a protocol amendment to an existing IND (per 21 CFR 312.305):

- The drug must be under investigation in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or all clinical trials of the drug have been completed.
- The sponsor of the IND supporting marketing must be actively pursuing marketing approval of the drug for the expanded access use with due diligence.
- The patient or patients to be treated must have a serious or immediately life-threatening disease or condition, and there must be no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.

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- The potential patient benefit must justify the potential risks of the treatment use and the risks of treatment use are not unreasonable in the context of the disease or condition to be treated.
- Providing the investigational drug for the requested use must not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Treatment Use of an Investigational Drug in Individual Patients, 21 CFR 312.310

The following additional requirements apply to use of investigational drugs for treatment of an individual patient by a licensed physician, including for emergency use.

- The treating physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and the patient cannot obtain the drug under another IND or protocol. If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor, by amending the IND to include the expanded access for the individual patient; or
- a licensed physician, by obtaining permission from the sponsor for FDA to refer to information in the IND to support the expanded access request and FDA with any other required information not contained in the IND (e.g., information specific to the individual patient).

Informed consent is important in treatment use situations because subjects may be desperately ill and particularly vulnerable. They may be receiving medications that have not been proven safe or effective. Both the setting and their desperation may work against their ability to make an informed assessment of the risks involved. As such, the IRB should seek to ensure that potential and actual subjects are fully aware of the risks involved in participation at all times.

Treatment use for a single patient is generally limited to a single course of therapy for a specified duration unless FDA authorizes multiple courses or chronic therapy. At the end of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

All expanded access uses are subject to FDA regulations for the protection of human subjects, including requirements for informed consent, unless the emergency use meets the criteria for FDA exception from general requirements for informed consent; IRB approval unless the emergency use meets the criteria for the exemption from the requirements for IRB review for emergency use; IND applications; and applications to market a new drug; and biological products.

See 21 CFR 312.305 for more information about FDA requirements for submission for expanded access use, safeguards, and when treatment may begin.

Treatment Use of an Investigational Drug in an Intermediate-sized Population, 21 CFR 33.315

Under specific conditions, FDA allows use of an investigational drug for the treatment of more than one patient when the population is smaller than that typical of a treatment IND or treatment protocol (as described below). For example, when a significant number of requests arise for individual patient expanded access to an investigational drug for the same use, FDA may ask a sponsor to consolidate the expanded access uses. In this situation, prospective IRB approval and informed consent is required.

Treatment uses for intermediate populations may arise when a drug

- is not being developed (e.g. rareness of disease/condition restricts recruitment);

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- is being studied in a clinical trial but patients requesting use of the drug are unable to participate in the trial; or
- is approved but is no longer marketed for safety reasons or is otherwise unavailable through marketing.

In addition to the criteria for all expanded uses (above), expanded uses in intermediate-sized populations require:

- there is enough evidence that the drug is safe at the dose and duration proposed for the expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and
- at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

See 21 CFR 312.315 for more information about submission requirements, and safeguards for this type of expanded access use.

Drugs for Treatment Uses for Persons with Life-Threatening and Severely-Debilitating Illnesses, 21 CFR 312.80 (Subpart E)

Subpart E of FDA regulations for Investigational New Drug Applications (IND), describes procedures to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. The decision to allow treatment or expanded uses of drugs for life-threatening and severely-debilitating illnesses for a single subject or a group of subjects is based on the following considerations:

- When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses.
- Benefits of a drug should be evaluated in light of the severity of the disease being treated.

Emergency Use IND

Important Note: At this time, UNLV does not actively conduct or manage planned emergency research; as such, UNLV does not have policies in place for such research. PIs interested in conducting planned emergency research must contact ORI-HS to discuss the possibility of engaging in this type of research.

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use with the requirement for the sponsor to file an appropriate application as soon as practicable. Prospective IRB review is required unless:

- all of the conditions for "emergency use" described above and at 21 CFR 56.102(d) are met; and
- all of the conditions are met for an FDA exemption at 21 CFR 56.104(c)

FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval.

Note: The IRB may determine it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review this use of the test drug.

Note: Under DHHS regulations, emergency use of an investigational drug is not considered research. Patients receiving the drug are not considered research participants and the outcome of emergency use of

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an investigational drug cannot be included in any report of a research activity subject to DHHS regulations. Under FDA regulations, the emergency use of an investigational drug is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

Informed consent must be obtained unless the conditions for exception from general requirements for informed consent at 21 CFR 50.23 are met.

Criteria for FDA Exceptions from General Requirements for Informed Consent for Emergency Use, 21 CFR 50.23

Physician-investigators must obtain legally effective informed consent as required by the IRB unless an FDA exception for informed consent at 21 CFR 50.23 (a) or (b) applies. The following two exceptions are relevant to emergency uses of test articles. The required documentation for both of these requirements must be submitted to the IRB within 5 working days after the use of the test article.

FDA Exception per 50.23(a): Informed consent is deemed feasible unless before use of the test article, both the investigator and a physician who is not otherwise participating in the clinical investigation certify (in writing) all of the following are true:

- The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time is not sufficient to obtain consent from the subject's legal representative.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

FDA Exception per 21 CFR 50.23(b): If it is the opinion of a clinical investigator that immediate use of the test article is required to preserve the life of the subject, and time is not sufficient to obtain the determination of an independent physician as described above prior to using the test article, the article may be used if within 5 working days after the use of the article, the clinical investigator's determinations are reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

BIOLOGICS

Human research with potentially hazardous biological agents requires additional safeguards, including review and approval by the UNLV's Institutional Biosafety Committee (IBC) *in addition to* review and approval by the IRB.

Potentially hazardous biological agents include but are not limited to the following:

- recombinant or synthetic nucleic acid molecules*;
- cells or viruses containing recombinant or synthetic nucleic acid molecules;
- microorganisms/infectious agents including non-virulent and vaccine strains (e.g., bacteria, fungi, parasites, viruses, prions);
- biologically derived toxins or toxic products including mutated, truncated, or inactivated toxins;
- allergenic extracts when used for diagnosis or intervention;
- select agents per the Federal Select Agent Program (additional approvals apply);
- human blood, body fluids, tissue, or cells/cell lines (including those used for transplantation);
- non-human (animal) blood, fluids, tissues or cells;
- plants, and plant tissues or plant cell cultures;
- insects, and insect tissues or insect cell cultures; and

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- animals infected with human pathogens or as sources of zoonotic diseases (i.e., diseases that can be transmitted from animals to people).

When an IRB proposal is submitted for review which include any of the biological agents listed above, it will ask about the status of an IBC approval. A concurrent review with the IBC is allowed. IRB approval is not contingent upon approval by the IBC.

The IRB reviews consent documents to ensure compliance with the following requirements for informed consent:

- DHHS OHRP at 45 CFR 46.116,
- FDA at 21 CFR 50.25,
- NIH (compendium of NIH resources on informed consent) where applicable

Both the IRB and IBC will review unanticipated problems, serious adverse events, changes in protocol, informational items or updates submitted during the course of the research, if appropriate.

Both IRB and IBC will review and follow reporting requirements and communication with PI's, sponsor, NIH Office of Biotechnology Activities, FDA, and OHRP.

Additional Requirements for Research Involving Nucleic Acid Molecules

NIH requirements (see NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules) apply to the following types of research involving recombinant or synthetic nucleic acid molecules in the U.S:

- Research that is conducted at or sponsored by an institution that receives NIH support for recombinant or synthetic nucleic acid research; and
- Research developed with NIH funds that involves testing in humans of materials containing recombinant or synthetic nucleic acids.

NIH defines the following categories of nucleic acid molecules:

- *Recombinant nucleic acid molecules*: molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell.
- *Synthetic nucleic acid molecules*: nucleic acids or molecules that are chemically or by other means synthesized, amplified, or modified that can base pair with naturally occurring nucleic acid molecules).
- Molecules that result from the replication of recombinant or synthetic nucleic acid molecules.

NOTE: Some types of molecules are exempt from the NIH guidelines.

Additional regulations apply to the deliberate transfer into human research participants of either recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or synthetic nucleic acid molecules. Specifically, no research participant shall be enrolled until the:

- IBC approval (from the clinical trial site) has been obtained
- IRB approval has been obtained.
- NIH Recombinant DNA Advisory Committee (RAC) review process has been completed (if applicable).

All *Human Gene Transfer* clinical trials are subject to FDA requirements for biological products and must comply with the additional informed consent requirements as specified in NIH guidelines for informed consent for human gene transfer trials.

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5. References

21 CFR 50, 56, and 312.

- International Conference on Harmonization (ICH) guidance for industry, E6 Good Clinical Practice: Consolidated Guidance (Good Clinical Practice Guidance).