Policy:
It is the policy of the UC Irvine (UCI) Institutional Review Board (IRB) that the use of investigational drugs, agents, and/or biologics be reviewed and approved for use in accordance with the federal regulations (FDA and DHHS).

I. UCI IRB Requirements for the Use of an Investigational Drug, Agent, or Biologic
   A. The UCI IRB conducts initial approval and on-going monitoring of all investigational drugs, agents, and biologics used in human subjects research under its authority.
   B. Prospective IRB review is required even if a waiver from IRB regulations has been granted by the FDA for use of the investigational drug, agent, or biologic.
   C. Research that involves the use of a drug other than a marketed drug in the course of medical practice must have an Investigational new drug (IND) number, unless the protocol meets the five exemptions from the requirement of an IND per 21 CFR 312.2(b).
      1. The criteria is as follows:
         a) Use of the investigational drug, agent, or biologic is not intended to be reported to the FDA in support of a new indication for use nor support any significant change in labeling for the product;
         b) The use of the investigational drug, agent, or biologic is not intended to support a significant change in the advertising of the product;
         c) The use of the product does not involve a route of administration, dosage level, and/or use in a subpopulation, or other factors that significantly increase the risks, or decrease the acceptability of the risks associated with the use of the drug, agent, or biologic;
         d) The use will be conducted in compliance with the IRB approval and informed consent procedures;
         e) The use will be conducted in compliance with the requirements concerning the promotion and sale of the drug, agent, or biologic as described in FDA regulations 21 CFR Sec. 312.7;
      It is important to note that the above does not intend to invoke exception from informed consent requirements for emergency use.
   D. FDA regulations allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods:
      1. Compassionate Use: The term “compassionate use” is erroneously used to refer to the provision of investigational drugs outside of an on-going clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term “compassionate use” does not, however, appear in FDA or DHHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials. Prospective IRB review and approval is required.
      2. Group C Treatment Investigational New Drug (IND): The "Group C" treatment IND was established by agreement between the FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents...
to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, the UCI IRB requires prospective IRB review and approval.

3. **Open – Label Protocol:** A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.

4. **Parallel Track:** A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that “parallel” the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the DHHS may, on a protocol-by-protocol basis, waive the provisions of 45 CFR Part 46 where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the UCI IRB.

5. **Treatment IND or Biologics:** A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Prospective IRB review and approval is required.

1. There are four requirements that must be met before a treatment IND can be issued:
   a) The drug is intended to treat a serious or immediately life-threatening disease;
   b) There is no satisfactory alternative treatment available;
   c) The drug is already under investigation or trials have been completed; and
   d) The trial sponsor is actively pursuing marketing approval.

2. The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:
   a) **Informed Consent.** Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, the IRB ensures that potential subjects are fully aware of the risks involved in participation.
   b) **Charging for Treatment INDs.** The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB
Committee pays particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB balances this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

6. **Single-Patient Use:** The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval by an IRB Chair is required.

7. **Emergency IND:** The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or biologics. Additional UCI IRB guidance regarding emergency IND is provided in IRB Policy 45.

8. **IND Exemptions in the Treatment of Cancer:** The FDA allows for an Investigational New Drug (IND) exemption of studies of lawfully marketed drug products for the treatment of cancer. When determining if an IND needs to be submitted to study marketed drugs for treating cancer, Researchers must apply the exemption criteria listed in 21 CRF 312.2(b)(1)(i-v). Additionally, planned studies may be considered exempt from the requirements of an IND if the studies involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a patient population with cancer and the following conditions apply:
   a) The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
   b) The studies are not intended to support a significant change in the advertising for the product.
   c) Investigators and their IRBs determine that, based on scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the drug product.
   d) The studies are to be conducted in compliance with the IRB and informed consent regulations, pursuant to parts 50 and 56.
   e) The studies will not be used to promote unapproved indications in compliance with 21 CFR 312.7.

E. Where a protocol is subject to review under more than one department or agency's regulations, the requirements of each set of regulations must be met. This situation may arise, for example, with Treatment Investigational New Drugs where both the FDA and DHHS have jurisdiction over the research. The use of an unapproved investigational drug, agent, and/or biologic requires an FDA IND.

II. **Use of an Investigational Drug, Agent, or Biologic by a Researcher**
   A. In order for an investigational drug, agent, or biologic to be used in clinical research at UCI, an IND number must be issued by the FDA.
B. A valid IND number is required (e.g., listed on Sponsor Protocol or a copy of the FDA approval of the IND). The UCI IRB will review research without an IND number but will not grant approval until documentation of an IND number is provided to the IRB.

C. Researchers provide information regarding the use of investigational drugs, agents, and biologics as required in the Appendix J of the IRB Application for human research.

D. Clinical investigations of a drug, agent, or biologic that is lawfully marketed in the United States are exempt from the requirements of an IND as per 21 CFR 312.2(b).

E. Research involving combinations of FDA approved drugs, agents, or biologics that are currently approved as single use, do not require an IND. However, use of these drugs, agents, or biologics in clinical research must still be prospectively reviewed and approved by the IRB.

F. The Investigator administering an investigational drug, agent or biologic must meet the following requirements in order to use an investigational drug, agent, or biologic in research conducted under the jurisdiction of the UCI IRB:

1. The drug, agent, or biologic must be used only in accordance with the plan of investigation as described in the FDA-approved IND application and the IRB-approved protocol;
2. The drug, agent, or biologic may only be used in participants under the LR’s supervision or under the supervision of a physician who is a Co-Researcher; and
3. Informed consent from the participant or the participant’s surrogate decision-maker is prospectively obtained, unless a waiver of consent has been approved by the UCI IRB.

G. Investigators using an investigational drug/biologic are required to provide a plan about how the drug/biologic will be managed and controlled in Appendix J of the IRB Application. Investigators are required to:

1. Describe how the Investigator will ensure that the investigational drug/biologic is used only in accordance with the UCI IRB approved protocol.
2. Explain how records for control of the drug/biologic will be recorded. For example, use of the sample Drug/Biologic Accountability Log provided on the Human Research Protections website; use of the Drug/Biologic Log provided by the Sponsor; or no log will be used and the researcher must provide justification.

H. Research with the use of an investigational drug, agent, or biologic must be conducted in accordance with all UC, UCI and UCI IRB policies and procedures.

I. All initial requests for IRB approval of a study that include the use of an investigational drug, agent, or biologic will be reviewed and approved by the full IRB Committee.

III. Use of an Investigational Drug, Agent, or Biologic by an Investigator Assuming the Sponsor Function

A. In rare instances, a UCI Investigator will assume the Sponsor function for use of an investigational drug, agent or biologic. A Sponsor-Investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

B. In addition to the requirements above, the UCI Investigator must submit a copy of the FDA Notice of Claimed Investigational Exemption for a New Drug (IND Application) along with their IRB protocol application for review. UCI IRB approval will not be granted until documentation of a valid IND number is submitted to the IRB.
C. The UCI Investigator must comply with all Sponsor function requirements described in 21 CFR 312.

IV. Advertising or Recruitment for Studies Involving Investigational Drugs, Agents, or Biologics (Also See IRB Policy 22)
A. Advertisements or recruiting tools must not include the term “new treatment”, without explaining that the drug, agent, or biologic is “investigational”, meaning non-FDA approved. A phrase such as “receive new treatment” implies that all study subjects will be receiving newly marketed products of proven worth. It is not a treatment since its effectiveness has not been proven or established. The term “new” is misleading as it gives the participant hope of a new intervention when the outcome is unknown. This could be viewed as coercive.
B. Advertisements or recruiting materials must not include the promise of “free medical treatment” when the intent is only to say that participants will not be charged for taking part in the investigation or experimental intervention (e.g. drug, agent, biologic). The use of the word “free” could be viewed as unduly influential as it may entice someone to participate in a study for the perceived benefits.

V. Informed Consent in Research that Involves an Investigational Drug, Agent, or Biologic
A. Informed consent must meet the requirements outlined in the IRB Informed Consent policies and procedures (See HRP Policy # 30);
B. No claims are made which state or imply, directly or indirectly, that the investigational drug, agent, or biologic is safe or effective for the purposes under investigation or that the drug is in any way superior to another drug;
C. The informed consent document must contain a statement that the drug, agent, or biologic is “investigational” or “experimental”;  
D. The informed consent document must contain a statement that the FDA may have access to the participant’s medical records as they pertain to the study; and
E. The researcher must assure that throughout the consenting process and study participation the participant understands that the investigational drug, agent, or biologic is under investigation, and that its benefits for the condition under study are unproven.

References:
21 CFR 50  
21 CFR 56  
21 CFR 210  
21 CFR 211  
21 CFR 312  
45 CFR 46  
FDA Guidance Sheet: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer, January 2004
Procedure: 41.A
Title: Procedure for Review of Research Involving Investigational Drugs, Agents, and Biologics

Procedure:
This procedure outlines the review and approval process for use of investigational drugs, agents, and biologics in clinical research.

I. Lead Researcher (LR) Responsibilities
   A. The LR will provide all information regarding the use of investigational drugs, agents, and biologics as required in the UCI IRB “IRB Application” (Appendix J). This will include the identification of the IND number.
   B. When the LR holds the IND for the investigational drug, agent, or biologic, a copy of the FDA approval letter is required as part of the IRB submission.
   C. The LR must provide justification for each of the conditions required for a drug, agent, or biologic to be exempt from the requirements of an IND (See HRP Policy # 41) The IRB Committee will determine if the justification warrants exemption from IND requirements.
   D. The Investigator will obtain the drug, agent, or biologic from the supplier.
      1. The product(s) will be sent to the UCIMC Pharmacy Specialist for Research, if they will be managing the storage, handling, and dispensing of the product(s); or
      2. The product(s) will be inventoried and managed by the Investigator and his/her staff as described in the Appendix J.
   E. The LR will complete the informed consent process, unless a waiver has been granted by the IRB.
   F. The LR will maintain all study case report forms and drug dispensing records as required by the sponsor, Institution, and/or FDA.
   G. The LR will notify the IRB of any modifications, unanticipated problems to participants or others that may occur while conducting the research or follow-up.
   H. The LR will assure that unanticipated problems involving participants or others are reported to the IRB via the UCI “Unanticipated Problems” (UP) application in accordance with HRP Policy # 19.
   I. The LR will complete and submit continuing reviews in accordance with HRP policy at the designated review intervals imposed by the IRB.
   J. The LR is encouraged to use the UCIMC Pharmacy Specialist for Research for dispensing of investigational drugs but may dispense from their department if the research takes place on the UC Irvine campus using proper handling, dispensing and storing techniques. Some of the requirements may include:
      1. Keeping a log of all drugs dispensed;
      2. Storing the drug in a double-locked cabinet or refrigerator at the temperature specified in the protocol or investigator’s drug brochure; and
      3. Sending the remaining drug back to the sponsor upon completion of the study.
   K. The Investigator will notify the FDA and IRB of closure or completion of the study and return all unused products per the sponsor’s instructions.

II. IRB Committee Responsibilities
   A. All initial requests for IRB approval of a study that includes the use of an investigational drug, agent, or biologic will be reviewed and approved by the full IRB Committee.
   B. When research involves a drug with an IND, the IRB Committee, together with the IRB Administrator, should evaluate whether the IND number is valid. The purpose of this
verification is to prevent situations where researchers may begin FDA-regulated research that require an IND before the FDA has issued an IND number.

C. If the LR is requesting the drug, agent, or biologic be exempt from IND requirements, the IRB Committee must discuss each of the conditions for an exemption and determine if the LR’s justification meets the criteria for exemption from the IND requirements.

D. The assigned reviewers of the research protocol involving drugs, agents, or biologics will seek clarification from a UCIMC pharmacy representative of any concerns that may affect the risk/benefit assessment.

E. The full IRB Committee will review the proposed research, informed consent documents (including notification that the FDA may have access to the participant’s study records), the procedure for obtaining informed consent, and additional information, when applicable, to determine whether the study meets criteria 45 CFR 46.111 and 21 CFR 56.111 for approval. In order to provide written documentation, the primary and secondary reviewers must complete the “IRB Reviewer’s Checklist” specifying that the criteria are met. The IRB Committee must first consider whether the protocol is scientifically sound. The following aspects of the study should be considered when making a determination regarding risk/benefit ratio:

1. Prior reviews by the FDA, other institutions, scientific review committees, funding agencies (e.g., NIH), or others; and
2. Study design which includes the study population, the trial phase, and mechanisms for data analysis and surveillance.

F. Submission of modifications, unanticipated problems to participants or others, and continuing reviews will be reviewed at the level for which the criteria are met.

III. IRB Administrator Responsibilities

A. The Administrator will pre-review and request any necessary revisions for submitted documents for use of investigational drugs, agents, or biologics as outlined for new IRB applications.

B. The Administrator will verify that additional documents have been submitted by the LR as required:
   1. Any supplemental information regarding the investigational drug, agent, or biologic supplied by the sponsor.

C. When research involves a drug with an IND, the IRB Committee, together with the IRB Administrator, should evaluate whether the IND number is valid. Validation of an IND can be done by:
   a) Determining that the IND number listed in Appendix J matches the Sponsor Protocol or
   b) Upon receipt of communication from the Sponsor, which corresponds with the IND number provided in Appendix J or
   c) Upon receipt of communication from the FDA, which corresponds with the IND number provided in Appendix J

Validation of an IND should not involve:
   d) Confirmation of the IND number by referencing the Investigator’s Brochure. This is because one IB often serves multiple IND’s.

D. Once the LR has met all the requisite requirements, the Administrator will place the new study on the next available Committee agenda, assign reviewers and prepare the reviewer and Committee packets.

E. If the LR is requesting the drug, agent, or biologic be exempt from IND requirements, the Administrator must document the IRB Committee’s discussion and determination for each of the conditions required for an exemption from the IND requirements.
F. The Administrator will assist reviewers in obtaining additional information that may be requested regarding the investigational drug, agent, or biologic from the LR.

G. The Human Research Protections (HRP) staff will process all requests for modifications, unanticipated problems to participants or others, and continuing reviews per corresponding IRB policies and procedures.

H. The HRP staff will update and maintain current information in the HPS database as applicable.