



UNIVERSITY OF CALIFORNIA, SAN DIEGO  
HUMAN RESEARCH PROTECTIONS PROGRAM

## FACT SHEET

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### Use of Chemicals that are not regulated by the FDA

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Research designed to understand mechanisms of health and disease may involve administration of substances that serve as markers or tracers for molecular events, or as physiologic stimuli. In some cases these substances may not be specifically manufactured for use in humans, and may not have been produced using FDA-approved methods (called Good Manufacturing Practice or GMP). In this circumstance an Institutional Review Board (IRB) must, under federal guidelines, accept responsibility for assuring that the substances used are safe for use in humans. These provisions of federal regulation have existed for many years, however national attention on this issue has been heightened as a result of the death of a normal volunteer exposed to an unapproved chemical at Johns Hopkins in 2001. This fact sheet is designed to provide researchers with information on the criteria that UCSD IRBs will use and require for their assessment of the safety of non-FDA regulated chemicals, including both substances given to induce a physiologic effect, and tracer substances administered in small quantities.

The UCSD Human Research Protections Program recognizes that substantial experience exists with the research uses of some chemicals as markers and stimuli, and that as a result they are generally recognized as safe. For other more novel agents there will be less experience, and a correspondingly greater need for analysis and documentation. UCSD IRBs will use the following criteria for review and approval of studies involving administration of non-FDA approved substances:

1. If the substance is available in a formulation that is listed in the U. S. Pharmacopeia (USP) as intended for

human administration, or is subject to FDA review and monitoring by virtue of having an Investigation New Drug (IND) number, no additional testing of the substance will be required. The investigator should describe the mechanism of action, intended use, and relevant safety information in the Research Plan submitted for IRB review, and include the USP or IND reference in the application.

2. If the substance to be used is not manufactured specifically for use in humans, and is neither USP listed or associated with an IND, the IRB will require that the application provide the following eight types of information and documentation
  - a. A review, based on the published literature, of the **mechanism of action, potential risks, and accumulated experience** with the use of the substance. If no animal or human safety data exists, the investigator must present safety data from a scaled dose test. Generally, a 500x scaled dose study in mice or rats will meet this requirement, but other model systems may be used depending upon the nature of the substance to be tested.
  - b. A statement, based on appropriate calculations, as to whether the substance will be administered in an amount that would be expected to have a **pharmacologic effect**. An estimate should be provided of the size of the dose to be administered relative to the total physiologic pool of the substance, in cases where tracers are used that are analogs of naturally

- occurring molecules. Most commonly this would be stated as a percentage of the total pool.
- c. A statement of the source (manufacturer) and whether the substance is synthetic or purified from biological sources.
  - d. Documentation of the **purity** of the substance to be administered. The preferred form of documentation is a Certificate of Analysis from an analytical laboratory. As a general rule, if the substance contains impurities, the nature of these impurities must be known and stated. Purity may be documented by standard methods such as mass spectroscopy and liquid chromatography. If a commercial laboratory is used, documentation should be provided that the laboratory uses FDA Good Laboratory Practice (GLP) methods. If assays of purity are performed by a noncommercial laboratory, the methods should be USP standard, and the appropriate USP methodology reference provided.
  - e. Documentation of the **sterility and pyrogen-free** characteristics of the specific batch(es) to be used in the research. The methods used in this determination should be included in the Research Plan, and follow USP methodologies, and/or be performed by a GLP laboratory.
  - f. Documentation, from published literature or specific testing (preferably using the same method as noted in c.), of the chemical **stability** of the substance.
  - g. A description of the **formulation** of the substance, including the physical description of the substance as received from the manufacturer, what solution the substance is dissolved in for administration, how it will be administered, and its expected toxicities.
  - h. For research involving **radioactive isotopes**, a separate application to the appropriate Radioactive Drug Research Committee (RDRC) -- either VA or UCSD-- is required. The RDRC will review the proposed use under criteria listed in federal regulation 21CFR361.1 and report its decision to the IRB. These criteria include both pharmacologic and radiation dose limits, and an assessment of whether the radiation exposure is justified on a risk-benefit basis.

Information relevant to items a-f above should be incorporated in the Section 8. Research Design and Methods component of the Biomedical IRB application, and any known risks associated with the administration of the test substance should be discussed in Sections 13 and 14 on Potential Risks and Risk Management Procedures, respectively.