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**RADIOLABELED DRUG PHARMACOKINETIC STUDIES
IN HUMANS IN THE UNITED STATES**

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General Requirements - Radioactive drugs for certain research uses are generally recognized as safe and effective when administered to human research subjects during the course of a research project intended to obtain basic information regarding the pharmacokinetics, distribution, metabolism and localization or regarding human physiology, pathophysiology and biochemistry, but not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness. The conditions under which use of radioactive drugs for research are considered safe and effective are: 1) Approval by an institutional Radioactive Drug Research Committee. 2) The pharmacologic dose of the active ingredients must be less than that causing any clinically detectable pharmacologic effect in humans. 3) The radiation dose must be the smallest dose with which it is practical to perform the study. 4) The radiation exposure is justified by the quality of the study and the importance of the information to be obtained. 5) The study meets the Food and Drug Administration (FDA) requirements regarding the qualifications of investigators, proper licensure for handling of radioactive materials, selection and consent of research subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions and approval by an appropriate Institutional Review Committee.

Rational for Use - In conducting pharmacokinetic studies it is necessary to choose the most sensitive methods available for determining absorption distribution, metabolism and elimination of the drug in question. Radioactive tracer studies utilizing isotope-labelled drugs are frequently the method of choice.

Regulation of Use of Radioactive Drugs - The FDA is the principal U.S. agency responsible for regulating the use of radioactive drugs as they affect human research subjects or patients. Certain authority to control radioactive materials is held by the

Federal Nuclear Regulatory Commission (NRC). The NRC generally follows basic radiation protection recommendations of the International Commission on Radiological Protection (ICRP) and its U.S. counterpart, the National Council on Radiation Protection and Measurements (NCRP). Guidelines followed for absorbed dose calculations are those of the ICRP or of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine. In order to handle investigational radioactive materials investigators and institutions must, in the case of reactor-produced isotopes, be licensed by the NRC or an Agreement State; in the case of non-reactor produced isotopes, be licensed by appropriate State or Local authorities when required by State Law.

Conduct of Studies Under an IND - Pharmacokinetic studies in the human with radiolabeled drug must be conducted under an Investigational New Drug Application (IND). This can principally be of two types: 1) a "Full" IND or, 2) an "Investigational" IND. Investigational sites can be: 1) Academic, 2) Hospital, 3) Government or 4) Commercial. The IND must be supported by nonclinical pharmacology, toxicology and pharmacokinetic data. The extent of information required is determined by study objectives, number of subjects/or patients and intended duration of drug administration. The nonclinical pharmacokinetic data must include absorption, distribution, metabolism, and excretion data in appropriate animal species with radiolabeled drug.