



MAR 27 1985

Dear Radioactive Drug Research Chairperson

Since the initiation of research with radioactive drugs in 1975 under 21 CFR 361.1, we have observed with satisfaction the acceptance and growth of the concept within the Nuclear Medicine community. Inevitably, as decisions by your committees have been made under the provisions of 21 CFR 361.1 and reviewed by FDA staff, some questions have arisen as to what the regulations would permit. In particular, there has been a tendency to try to utilize 361.1 to carry out early clinical trials of a radiopharmaceutical drug that properly are conducted under an IND. We would like to provide our views on these questions,

Part 361.1 designates certain research uses of radioactive drugs as "generally recognized as safe and effective". When a drug is generally recognized as safe and effective it is not a "new drug", as defined by the Food, Drug, and Cosmetic Act which states that a "new drug" is one "not generally recognized,....as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling..." When a "new drug" is used in humans and the drug is not yet approved for marketing an IND is required. No IND, however, is needed to study a drug that is not a new drug. The RDRC cannot provide an exemption from the act for new drugs, but can determine, under the specific requirements set forth in 361.1 that the drug to be used is, under the conditions specified by the investigator's protocol and approved by the committee, not a new drug.

The provisions of the RDRC regulations specifying how a committee can determine that a drug is "generally recognized as safe and effective" and, therefore, not a new drug, are detailed in 361.1. Let me address these briefly.

The type of research that may be undertaken with the drug must be intended to obtain basic information and not to carry out a clinical trial. The types of basic research permitted are specified in the regulation, and include studies of metabolism, human physiology, pathophysiology, or biochemistry. Types of research studies not permitted under this regulation are also specified, and include those "intended for (the) immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial)." The notice of proposed rule making for this regulation stated "the evaluation of the drug as a clinical tool, including comparison with other agents, should be considered as part of a clinical trial and subject to the requirements of 312.1.", i.e. require an IND, (Federal Register, Monday, July 29, 1974). Although the distinction is clearly stated, there can be areas of overlap between "research" and "clinical trial" studies. It is recognized, for

example, that the earliest studies showing localization of a drug in a particular organ or fluid space will have obvious relevance to the later trials; nonetheless, these early localization studies are considered basic research. We have reviewed RDRG-approved protocols, however, in which the evaluation of the drug as a clinical tool for particular organs or spaces was clearly the research objective. While, the distinction is not always clearcut, where doubt exists as to whether the research proposal is basic research, as defined in the regulation, the drug should be considered a new drug for which an IND is required.

The limitation on radiation dose is clearly stated and some have felt that these limits mean that FDA has determined these radiation doses to be safe. The FDA does not feel that any dose of radiation is absolutely safe, or that higher doses than those proposed are necessarily unsafe. There was a need for the purposes of this regulation to find some reasonable level below which the radiation doses would present minimal risk. Based on the radiation dose limitations established by NRC for basic occupational radiation protection (10 CFR 20.101 and 20.102), we proposed these as levels below which a drug could be considered as not a new drug, so long as all other portions of the regulations were met.

Although methodology is specified in the regulation by which radiation dose estimates are to be derived and reported, with special attention to whole body, active blood forming organs, lens of the eye, and gonads, taking into account the contribution of radiocontaminants and other radiation exposure procedures associated with the study, the reporting has frequently been incomplete. The total calculated radiation dose exposure per study must include all aspects of exposure, including X-Ray examinations and other isotope procedures related to the study. This should also include the radiation dose from possible radiocontaminants. The method of calculating the radiation exposure should be one that estimates a "worst case" situation as we would like to have adequate evidence that the radiation dose levels will not be exceeded. With radiopharmaceuticals in early investigation, adequate biodistribution data may not be available or may be equivocal so that the committee may not be able to establish that the radiation dose limits will not exceed the levels set by the regulation. Available methodology may also leave uncertainty as to whether radiation dose to the critical organs will be within the specified limits. Where the committee cannot be certain that the radiation dosage criteria will be met, an IND should be sought.

Similar reasoning extends to the limitations on pharmacologic dose which "shall be known not to cause any clinically detectable pharmacologic effect in human beings." For the committee to conclude that this criterion has been satisfied, there must be pharmacologic data available from studies in human subjects that would form the basis of the committee's action. If no data are

available, even the smallest amount of the drug must be assumed to produce pharmacologic activity, and an IND should be sought.

Once approved, the study should be the subject of continuing review at the committee's quarterly meetings so that it does not evolve into a research project that no longer satisfies the criteria for RDRC approval. Reports of the progress of approved studies are made to us yearly, but there is a requirement for immediate reporting if the study involves exposure of more than 30 research subjects or of any research subject under 18 years of age. This requirement has not been complied with in some cases, and we consider it important to our overview responsibility.

There are several other issues that have been the source of some confusion in the past:

- (a) The RDRC, as defined in 21 CFR 361.1 has no oversight responsibility or authority over an investigation carried out under an IND exemption. This authority is retained by the FDA. Title 21 CFR 361.1 however, does not in any way prohibit an institution from involving the RDRC in other policy matters, including the use of radioactive drugs, if it so chooses.
- (b) The RDRC is distinct from all other investigational drug review committees within an institution such as the radiation safety committee and the Institutional Review Board (IRB). The approval of both of these committees in addition to RDRC approval, is required before an RDRC investigation can be permitted to start.
- (c) The RDRC is established and chartered by the FDA under 21 CFR 361.1. It is not related to any specific type of license granted by the MPC or State-Regulatory bodies. These licensing authorities, of course, make their own regulations, rules, and requirements. For their own purposes they may make an RDRC a requirement for a specific type of license, but these are not requirements under 21 CFR 361.1.

In sharing these observations with you, I also invite your comments. My intent is to preserve and improve the implementation of the RDRC regulations.

Questions and comments should be directed to Mr. Neil Abel, a Reviewing Pharmacist and the Executive Secretary of the Radiopharmaceutical Drugs Advisory Committee to the FDA. His address is the Division of Oncology and Radiopharmaceutical Drug Products, Office of Drug Research and Review

(HFN-150), Food and Drug Administration, Center for Drugs and Biologics, 5600 Fishers Lane, Rockville, Maryland 20857.

Sincerely yours,

A handwritten signature in black ink that reads "Robert Temple". The signature is written in a cursive style with a large, sweeping initial "R".

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics