

January 14, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration, HHS
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re.: Request for Comments – **Docket No. 2004N-0432**

Dear Sir or Madam:

I am writing in response to the U.S. Food and Drug Administration's request for comments on the potential need to revise the FDA regulations (21 CFR 361.1) governing the operations of Radioactive Drug Research Committees (RDRC's), and to issues raised at the FDA's Public Meeting held November 16, 2004.

I am a board-certified (Board of Pharmaceutical Specialties) nuclear pharmacist currently employed at the Massachusetts General Hospital, where I serve as Director of Nuclear Pharmacy and Chair of the Radiation Safety Committee and Radioactive Drug Research Committee (RDRC #0032).

I offer the following comments for your review:

1. *Pharmacology Issues*: Section 361.1(b)(2) requires that the amount of radioactive drug to be administered be known not to cause any clinically detectable pharmacological effect in humans.

This limitation raises significant issues for RDRC's when they are presented with applications that provide minimal supporting data on the previous human experience with a particular compound. In many cases the only human experience may be with the radioactive form of the compound at other institutions from within or outside the United States. Less restrictive regulations in other countries often prompt investigators to obtain initial human experience offshore and then provide some testament of non-pharmacological effect based on this experience. Given that in most cases a scientifically valid pharmacological dose finding study has not been performed, the committee is faced with a decision to accept or reject such an application when it has knowledge of the safe and widespread use of the radioactive compound.

I am supportive of a revision to the 21 CFR 361.1 regulations to permit first-in-human studies of radioactive drugs administered at "microdose" levels. It seems more prudent to

base approval of a RDRC drug based on a prospectively designed animal toxicity study rather than some ill defined human experience as is occurring presently in many cases.

It is also recommended that the initial human subjects to be studied at the “microdose” levels would be monitored with standard physiological testing (vital signs, etc.) and general safety lab test monitoring (chemistry and hematology). Any suggestion of a pharmacological effect would be submitted to the RDRC for further action.

I support the revision of 21 CFR 361.1 regulations to implement these changes rather than development of a new set of regulations as discussed at the hearing for an as yet undefined “exploratory IND” process.

In a related discussion at the November 16 hearing, it became known that the FDA is aware of certain actions of specific RDRC’s that are in fact already approving first-in-human studies. These seemingly random acts involve the modification of a known molecular entity with foreign radionuclides and/or bi-functional linking entities. It has always been my position that such a practice is in direct violation of 21 CFR 361.1(b)(2) and has not been allowed under the MGH RDRC. The fact that this activity is known to the FDA and seemingly condoned is of great concern and is a disservice to RDRC’s who are making every attempt to fully comply with 21 CFR 361.1. Moreover, the willingness of the FDA to accept these situations while NOT allowing for a structured “microdosing” program is an unacceptable position.

The introduction of a foreign atom, radioactive or stable, into a molecule creates a new molecular entity that is likely to have different chemical and pharmacological properties. For example, in PET, the acetate molecule is routinely radiolabeled by substitution of a stable C-12 atom with a radioactive C-11 atom. Under the practice described above, the evaluation of F-18 labeled acetate might be approvable by some RDRC’s with FDA knowledge. While acetate ion is widely used in humans in a variety of pharmaceutical dosage forms, fluoroacetate is a highly toxic compound. It is estimated that the human LD50 of fluoroacetate is approximately 2-10 mg/kg. (Egekeze & Oehme 1979) This example of the potential change in behavior from a seemingly simple substitution that might be made for the purposes of radiolabeling should be evidence enough that this practice should not be condoned by the agency.

A much more logical approach is to allow first-in-human evaluation of radioactive drugs under a structured and monitored microdosing program under RDRC and FDA control.

2. *Radiation Dose Limits for Adult Subjects*: Radiation dose limits for adult subjects specified in Section 361.1(b)(3)(i) were based on occupational radiation protection criteria established by the Nuclear Regulatory Commission (NRC) under 10 CFR 20.101. Current trends suggest that the limits would be more appropriately expressed as a total “effective dose” rather than the organ and whole body limits currently specified. This would allow for more meaningful comparison and evaluation of all radiation doses to which a subject may be exposed (i.e. x-ray, CT, etc.) and would be in keeping with policies and procedures of many Institutional Review Boards in designing informed consent documents.

3. *Quality and Purity of the Radioactive Drug.* While Section 361.1 (d)(6) requires the RDRC to assure that the radioactive drug used in the research study meets appropriate standards of strength, quality and purity there is no further discussion as to what constitutes “appropriate standards” for the radioactive drug.

Currently, standards exist for both Positron Emitting i.e., USP Chapter <823>, *Radiopharmaceuticals for Positron Emission Tomography-Compounding*, and single photon emitting radiopharmaceuticals, i.e., <797>, *Pharmaceutical Compounding – Sterile Products*, compounded for human use. These standards appear under the auspices of the United States Pharmacopeia in the form of general chapters and individual product monographs, and, as official chapters and monographs, are enforceable by the FDA. As such, I recommend that 21 CFR 361.1 specifically identify the USP as the drug standard setting body for drugs approved under this section.

4. *RDRC Membership:* Under Section 361.1(c)(1), a RDRC must include the following expertise: (1) a physician recognized as a specialist in nuclear medicine; (2) a person qualified to formulate radioactive drugs, and (3) a person with special competence in radiation safety and radiation dosimetry.

While the areas of expertise are listed, no specific qualifications or professional licensure is stated other than for the nuclear medicine physician. Of specific concern to me is the individual who fulfills the required membership position under (2) above, i.e., a person qualified to formulate radioactive drugs.

Clearly, in the vast majority of cases, the drugs approvable under 21 CFR 361.1 are “formulated” in a manner that is significantly different from routine nuclear medicine practice, i.e., commercially available products used clinically. Specifically, radiopharmaceuticals used for PET require complex radiochemical synthesis with the subsequent formulation of a sterile injectable product that must be administered to subjects within a very short time after preparation. This specialized function requires skilled individuals who by nature of their training and experience are qualified to carry out these functions.

The undefined qualifications stated in this section currently could allow for this position on the RDRC to be held by a physician and/or nuclear medicine technologists. It is my firm belief that such individuals are unlikely to possess those skills necessary to perform this function in a meaningful way.

By nature of specialized training and education, the most appropriate individuals to fill this position on an RDRC are nuclear pharmacists. I strongly recommend that 21 CR 361.1 be revised to specifically name the nuclear pharmacist as a required member of the committee rather than the ill-defined requirement now in place.

It is likely that institutions conducting such RDRC approved research already have a nuclear pharmacist on staff. In the event that this is not true, outside consultants could meet this need.

In summary, I commend the FDA's action to revisit the RDRC regulatory process. The research currently being conducted under 21 CFR 361.1 is crucial to the better understanding of disease and in the development of new drugs to treat them. Every effort should be made to continue to promote such work in a safe and efficient manner without undue regulatory hurdles.

Please contact me if I can be of any further assistance.

Sincerely,

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