Food and Drug Administration
Center for Drug Evaluation and Research

Public Meeting
"Radioactive Drugs for Certain Research Uses"

November 16, 2004

Advisors and Consultants Conference Room 1066
5630 Fishers Lane
Rockville, MD 20857

Meeting Objectives

We are seeking public input on the need to modify the conditions set forth in 21 CFR 361.1 that would ensure the safe use of radioactive drugs for basic research purposes without an investigational new drug application (IND) in light of the numerous scientific and technological developments that have significantly impacted the use of radioactive drugs since the RDRC regulations were adopted in 1975. Specifically, we have the following questions for your consideration:

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. According to § 361.1(d)(2), investigators must provide pharmacological dose calculations based on published literature or other human data to demonstrate an absence of a clinically detectable pharmacological effect (thus, no radioactive drug may be studied "first in humans" under current § 361.1).

   A. For an active ingredient chemically manufactured in the laboratory that is also a body constituent (an endogenous substance), what percentage of estimated daily endogenous production could be considered to have no pharmacological effect? (Because heterogeneous biological products (e.g., monoclonal antibodies and therapeutic proteins such as interferon, interleukin, other cytokines, and enzymes) are foreign proteins and are assumed to have the potential to produce an antigenic response, they should be excluded from consideration unless they have been shown to have no immunologic response.)

   B. For an active ingredient that is not endogenous, what animal, in vitro, and/or in vivo data would be needed to demonstrate that there is no human pharmacological effect? Is there an absolute dose that would ensure no pharmacological effect? If so, what data would be needed to support that dose?

C. How may an investigator confirm that a radioactive drug causes no clinically detectable pharmacological effect in humans in accordance with § 361.1(b)(2)? What parameters should be measured, how frequently, and what criteria should be used to determine if a pharmacologic effect has occurred?

2. Radiation Dose Limits for Adult Subjects

The radiation dose limits for adult subjects specified in § 361.1(b)(3)(i) are based on the basic occupational radiation protection criteria established by the Nuclear Regulatory Commission under 10 CFR 20.101. FDA's thinking in 1975 was that these criteria would enable a potential research subject to make an informed decision regarding participation in a study under § 361.1 because the subject would, in effect, be deciding whether he or she was willing to assume the same risk as a radiation worker for the duration of the study. Considering the advances in scientific knowledge and regulatory changes that have occurred since 1975, including new data on radiation effects (Ref. 1) and new recommendations on radiation dose limits (Refs. 2, 3, and 4), are the current dose limits for adults still appropriate for research conducted under § 361.1? If not, what dose limits are appropriate? Should there be different dose limits for different adult age groups?

3. Assurance of Safety for Pediatric Subjects

Currently, § 361.1 allows for the study of radioactive drugs in subjects less than 18 years of age without an IND if:

- The study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, is without significant risk to subjects, and is supported with review by qualified pediatric consultants to the RDRC;

- The radiation dose does not exceed 10 percent of the adult radiation dose specified in § 361.1(b)(3)(i); and

- As with adult subjects, the following requirements, among others, are met: (1) The study is approved by an IRB that conforms to 21 CFR part 56, (2) informed consent of the subjects' legal representative is obtained in accordance with 21 CFR part 50, and (3) the study is approved by the RDRC that assures all other requirements of § 361.1 are met.

Alternatively, when a study is conducted under an IND in accordance with part 312, the sponsor must submit to FDA the study protocol, protocol changes and information amendments, pharmacology/toxicology and chemistry information, and information regarding prior human experience with the same or similar drugs (see §§ 312.22, 312.23, 312.30, and 312.31). Additionally, § 312.32 requires that sponsors promptly

review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic. This includes information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities. Section 312.32 also requires that sponsors submit IND safety reports to FDA.

A. Does § 361.1 provide adequate safeguards for pediatric subjects during the course of a research project intended to obtain basic information about a radioactive drug, or should these studies only be conducted under an IND?

B. If we assume that § 361.1 provides adequate safeguards for pediatric subjects during such studies, given our present knowledge about radiation and its effects, can we conclude that the current dose limits for pediatric subjects do not pose a significant risk? If not, what dose limits would be appropriate to ensure no significant risk for pediatric subjects? Should there be different dose limits for different pediatric age groups?

4. Quality and Purity

What standards for quality and purity should apply to radioactive drugs administered under § 361.1 to ensure the safety of research subjects?

5. Exclusion of Pregnant Women

Section 361.1(d)(5) requires that each female research subject of childbearing potential state in writing that she is not pregnant or, on the basis of a pregnancy test, be confirmed as not pregnant before she may participate in any research study involving a radioactive drug under § 361.1. Is written attestation adequate assurance that female research subjects are not pregnant? If not, what other assurance should be provided?

6. RDRC Membership

Under § 361.1(c)(1), an RDRC must include the following expertise: (i) A physician recognized as a specialist in nuclear medicine, (ii) a person qualified to formulate radioactive drugs, and (iii) a person with special competence in radiation safety and radiation dosimetry. Would an RDRC benefit from any additional expertise, such as a pharmacologist or toxicologist? Should such memberships be required?

Under § 361.1(c)(4), changes in the membership of an RDRC must be submitted to FDA as soon as, or before, vacancies occur on the committee. However, the regulations do not require approval of new members by FDA before a new member assumes committee responsibilities. We review the qualifications of new members when we receive them and contact the RDRC when we identify new members we

consider to be unqualified, but we do not always receive notifications of changes in membership in a timely manner. At times, this has resulted in unqualified members serving on RDRCs for extended periods. Should the regulations specifically require that FDA approve RDRC membership changes before new members assume committee responsibilities? For example, would it be appropriate for the regulations to allow FDA 15 days to review the qualifications of a proposed new member before the member could assume committee responsibilities?