

Division of Dockets Management
HFA-305
Food and Drug Administration
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No 2004N-0432: Radioactive Drugs for Certain Research Uses

This statement is being submitted by the Society of Nuclear Medicine on behalf of their membership. The comments herein pertain to the questions that were raised at the 16 November 2004 Public Meeting entitled "Radioactive Drugs for Certain Research Uses".

1) Pharmacology Issues

The current pharmacological requirements in the RDRC regulations provide adequate protection for human subjects under the RDRC process. As first-in-human studies are not permitted under the current RDRC regulations, we support the use of the Exploratory IND (E-IND) to evaluate new radiotracers in humans before proceeding with an RDRC application. It remains appropriate that documentation of first-in-human use of either the radioactive or non-radioactive compound of the same exact structure be required for using the RDRC mechanism. These data may come from many sources including but not limited to medical literature, data from another institution where imaging studies have been approved, Phase I study data or Exploratory IND data. We recommend that guidance documentation clarify the types of studies allowed under the RDRC regulations. As raised below in the RDRC membership section, a pharmacologist may participate on the RDRC as needed and when required.

2) Radiation Dose Limits for Adult Subjects

The present dose limits that are defined in 21CFR361.1 are over 30 years old. We support the conversion from whole body dose to "Effective Dose" with the use of tissue weighting factors. Allowing effective doses of up to 3 rem for a single study and 5 rem annually provides adequate protection for subjects participating in RDRC studies. There should be NO limitation on organ doses except to limit deterministic effects since the potential harms from stochastic effects are already accounted for in the calculation of effective dose. To prevent deterministic effects to individual organs, the dose equivalent to individual organs should be limited to 50 rem per year except a limit of 15 rem per year should apply to the lens of the eye.

We further recommend that future FDA regulations be issued with radiation doses in System International or SI units (Sievert, Gray) replacing traditional units (rem, rad).

3) Assurance of Safety for Pediatric Subjects

Obsolete and unduly restrictive language in the current regulations severely limits the use of the radiopharmaceuticals in children and adolescents under the RDRC mechanism. In particular, this obsolete and restrictive language limits the ability of researchers to apply new positron emission tomography (PET) and molecular imaging technology in the study of serious and often life-threatening or life-shortening pediatric diseases. It also restricts use of this technology in chronic debilitating neurologic and neuropsychiatric disorders.

The serious diseases that affect children are generally not encountered in adults. In the spectrum of pediatric cancer, only Hodgkin disease and high-grade lymphoma occur frequently in both pediatric and adult populations. The other common pediatric malignancies, including neuroblastoma, many sarcomas, and most malignant brain tumors that occur in children, are infrequently encountered in adults. Chronic neurologic conditions, such as uncontrolled seizures in a child, may severely limit function and prevent normal development. There is also a wide spectrum of pediatric congenital diseases that significantly reduce life expectancy and cause significant morbidity during the shortened lifetimes of the patients. In only about 25% of the practice of pediatric nuclear medicine at a large children's hospital do the indications and the imaging studies performed correspond to adult nuclear medicine practice. Similarly pediatric and adult nuclear medicine research needs are sometimes quite different.

The problems with the current RDRC regulations are three. First the radiation exposure limits are expressed in terms of whole-body dose, which is an obsolete concept. The current concept of effective dose (H_E) is more appropriate.

The second problem is that the pediatric dose limits hold the investigator to 10% of the adult absorbed dose. This limit does not allow needed research in patients who have cancer, and other chronic diseases that are life-threatening, debilitating or shorten life expectancy.

The third problem is that the target organ dose permitted is inappropriate in relation to the H_E or whole body dose.

Several changes are appropriate:

1. The H_E concept should replace the concept of whole body dose.
2. An upper limit for target organ dose is probably not necessary. The H_E calculation takes into account most of the risk associated with exposure to individual organs. If an upper limit is set for target organ dose, it should be 10 times higher than the H_E , not 1.6 times higher than the whole body dose.
3. The upper limit for H_E should be higher for children with cancer and other chronic life threatening, debilitating or life shortening diseases. These children are at much higher risk from the disease itself than from the theoretical risk of

exposure to a diagnostic radiotracer. An upper limit for H_E of 2.0 rem for total annual effective dose from use of experimental radiopharmaceuticals should be set for these patients in the revised RDRC. This will facilitate needed research with positron emitting radiopharmaceuticals and molecular imaging technology..

Research in pediatric patients with cancer and other life threatening or life shortening diseases should not be unduly restricted. These children, their families and children who will acquire these diseases in the future should be allowed to benefit as a group appropriately conducted research with diagnostic radiopharmaceuticals under the RDRC regulations. The regulatory environment should not move in a direction that will make it more difficult to use and advance this technology in the future. We do not want to see the creation of unnecessary regulatory impediments to pediatric research with radiopharmaceuticals, rather we wish to see appropriate adjustments made that will facilitate research with diagnostic radiopharmaceuticals in children and adolescents with cancer and other chronic life shortening, debilitating or life threatening diseases.

4) Quality and Purity

In accordance with Section 361.1 (d)(6), the RDRC is required to assure that the radioactive drug used in the research study meets appropriate standards of strength, quality and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the study. There is, however, no further discussion as to what constitutes “appropriate standards” for the radioactive drug.

There are currently several standards used by radiopharmaceutical producers. The FDA is finalizing the CGMP guidance. There are also two USP chapters that cover radiopharmaceutical compounding, Chapter <823> for PET radiopharmaceuticals and Chapter <797> for non-PET radiopharmaceuticals. Additionally there are several USP monographs for radiolabeled compounds.

We support the use of USP <823> and <797> as standards for the non-commercial preparation of radiopharmaceuticals which would cover most applications carried out under the RDRC purview. The CGMP rules would apply to the preparation of radiopharmaceuticals for commercial distribution.

5) Exclusion of Pregnant Women

Given the small risk to the fetus, written attestation by the patient that she is not pregnant should be sufficient for radiation doses that are less than a few mSv. Requiring serum or urine pregnancy tests in all woman who have the potential to bear children is reasonable if fetal doses are likely to exceed 10 mSv.

6) **RDRC Membership**

The FDA has raised the question of the benefit to the RDRC by the addition of individuals with expertise in pharmacology. Given that the RDRC regulations do not permit first in human studies and that adequate pharmacology will have been performed and demonstrated either under the Exploratory IND or IND processes, we feel that it is not necessary to add a pharmacologist as a standing member of the RDRC. The RDRC, however, should be encouraged to include ad hoc members to support the review of individual protocols as needed. Thus the membership that is currently prescribed by 21 CFR 361.1 is sufficient.

In response to the questions regarding FDA approval of the RDRC members, we support the review of RDRC members by the FDA. Once a new member has been added to the RDRC, either through initial chartering of a new RDRC or by filling a vacancy created by loss of a committee member on an existing RDRC, the RDRC should submit the CV of the proposed new member to the FDA for approval. The FDA should notify the RDRC within 30 days of receipt of the CV as to the status of the new member. Once approved by the FDA the member may join the RDRC. If the FDA fails to respond within the 30 days then the proposed member should become a full member of the committee.

General Comments:

During the comment period there have been several public discussions of needed changes in the RDRC regulations. Some of these discussions have brought up issues that should be clarified in the revised regulations.

One issue is “strict” versus “liberal” interpretation of the language in 21 CFR 361.1 (a) stating that studies performed under the RDRC regulations should be “intended to obtain basic information regarding the metabolism (including kinetics, distribution and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for 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 new regulations should clearly state that a drug may be studied under the RDRC regulations to determine if there is abnormal metabolism or receptor binding of the radioactively labeled drug in either normal or abnormal tissues. Such studies of metabolism and/or receptor binding would be smaller in scope than a clinical safety and effectiveness study. Questions reasonably answered under the RDRC regulations should include “Does radiopharmaceutical A demonstrate abnormal metabolism in a diseased organ or tissue?” “When radiopharmaceutical B is used to measure a specific metabolic property of a tumor, does a single cycle of chemotherapy change the tumor’s metabolism as measured by radiopharmaceutical B (with the requirement that the results will not be used to make therapeutic decisions)?” “In a disease of the central nervous system, which tissues in the brain have abnormal binding of radiopharmaceutical C that is known to bind with certain neuroreceptor?” The new regulations should clearly state that studies of abnormal physiology and abnormal tissues and organs are permitted

uses. We argue in favor of clearly stated regulations that acknowledge and permit the large amount of research that has been performed safely under the RDRC regulations over the last three decades, but stopping short of permitting clinical decision making or the performance of entire clinical safety and effectiveness studies under the regulations. The revised regulations should take into account the actual application of the current regulations throughout the U.S.

Another issue is use of the RDRC mechanism in the patients under age 18 years. It has been argued by an FDA staff member that all pediatric studies should be done under an IND. We believe that this is an incorrect interpretation of the current regulations and that the revised regulations should continue to permit pediatric studies under the RDRC regulations without an IND. 21 CFR 50.53 considers "Clinical investigations involving risk greater than minimal risk and no prospect of direct benefit to the patient, but likely to yield generalizable knowledge about the subjects' disorder or condition. Such investigations are permitted under 21 CFR 50.53 "if the IRB finds and documents that: (a) the risk involves only a minor increase over minimal risk". And "(b) that the ... procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical ... situations." We believe that studies under the RDRC regulations in patients under 18 years of age conform to Part 50.53. The risk is slightly more than minimal risk, but not a significant risk. In patients, with cancer and other life threatening and life shortening diseases, the experience of nuclear imaging and the absorbed radiation are similar to other imaging procedures routine experienced by these patients. For example, as part of the treatment protocol, a patient with cancer may undergo 5 CT examination of the chest, abdomen and pelvis in a 12 month period with a total effective radiation dose from the CT studies of 5 rem or more, including 5 venipunctures and 5 administrations of intravenous and oral contrast material. The impact on the patient of one or two PET imaging studies on the patient from the standpoint of discomfort and theoretic radiation risk will be less than impact of conventional imaging. "More than minimal risk" studies in normal subjects under 18 years of age or in children with diseases that are not life-threatening or life shortening would continue to be subject to the IRB regulations in Part 50.

Respectfully submitted on behalf of the Society of Nuclear Medicine by

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