



2306 5 JUL -8 110:52

Department of Radiology

July 7, 2005

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

Dear Sirs:

As a physician involved in pediatric imaging research, including pediatric nuclear medicine and molecular imaging, I would like to comment on the upcoming re-write of the Radioactive Drug Research Committee (RDRC) regulations. Obsolete and unduly restrictive language in the current regulations severely limits the use of the radiopharmaceuticals in children and adolescents under the RDRC regulations. 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 often 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.

2004N-0432

Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021
NCI-designated Comprehensive Cancer Center

C10

The second problem is that the pediatric dose limits hold the investigator to 10% of 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.

The two attached "Background" pages illustrate the limitations of the current regulations in greater detail. There is not a single PET agent used clinically or experimentally for cancer imaging that meets the 0.5 rem limitation on target organ dose. In fact, almost all PET and single photon emitting radiopharmaceuticals used for clinical imaging will have a target organ dose of more than 0.5 rem. When administered in amounts that are large enough to permit studies of adequate quality from a quantitative and qualitative standpoint, fluorine-18 labeled radiopharmaceuticals generally have H_E of 0.5 to 1.0 rem.

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 diseases that are life threatening, debilitating or life shortening. 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 regulations. This will facilitate needed research with positron emitting radiopharmaceuticals and molecular imaging technology.

During the comment period there have been several public discussions of needed changes in the RDRC regulations. Some of these discussions have brought up important 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 quantitative measurements of the uptake of 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, i.e., pathophysiology, are permitted uses. The revised regulations should take into account the actual application of the current regulations throughout the U.S. 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.

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. I 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 examinations 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 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. The IRB regulations in Part 50 are compatible with the RDRC concept and also prevent an IRB from approving inappropriate research in subjects under 18 years.

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 in subpharmacologic amounts under the RDRC regulations. The regulatory environment should not move in a direction that will make it more difficult to use and radioactive tracer technology in the future. In the last 3 decades, the long-term survival rate for pediatric cancer has increased from a few percent to approximately 75%. Children with cancer are particularly likely to benefit from the use of molecular imaging technology; new approaches to the cure of cancer will come from novel therapies backed by new diagnostic techniques. We do not want to see the creation of unnecessary regulatory

Background

21CFR361.1 (b) (3) (i) states with reference to studies performed under approval by a Radioactive Drug Research Committee:

“Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such dose exceeds the following:”

Whole body, active blood forming organs, lens of eye and gonads	
single dose	3 rem
annual and total dose commitment	5 rem
Other organs	
single dose	5 rem
annual and total dose commitment	15 rem

“For a research patient under 18 year of age at his last birthday, the radiation dose shall not exceed 10% of that set forth in paragraph (b) (3) (i).”

The pediatric limits, therefore, become:

Whole body, active blood forming organs, lens of eye and gonads	
single dose	0.3 rem
annual and total dose commitment	0.5 rem
Other organs	
single dose	0.5 rem
annual and total dose commitment	1.5 rem

These limits greatly limit the ability to study new PET agents in children with cancer or other life threatening diseases. Absorbed radiation doses for most PET radiopharmaceuticals exceed 0.3 rem whole body and 0.5 rem to any other organ. The limits may also pose a problem for studies using SPECT radiopharmaceuticals. Target organ doses will always be considerably greater than 1.6 times the H_E or whole body dose. [Ref: Stabin MG, Gelfand MJ. Q J Nucl Med 1998: 42:93-112.]

Some examples of H_E , effective dose equivalent (H_e) and target organ dose for PET radiopharmaceuticals are:

[F-18] 2-fluoro-2-deoxyglucose

For 9.8 mCi in a 70 kg adult	H_E 0.88 rem;	bladder wall 6.8 rem
For 4.5 mCi in a 10 year old	H_E 0.64 rem	bladder wall 3.6 rem
For 2.6 mCi in a 5 year old	H_E 0.56 rem	bladder wall 3.0 rem

[Ref: Stabin MG, Gelfand MJ. Q J Nucl Med 1998: 42:93-112.]

[F-18] fluorocholine

For 7.7 mCi in a 70 kg adult	H_E 1.0 rem	kidney 2.46 rem
------------------------------	---------------	-----------------

[Ref: DeGrado TR, et al. J Nucl Med 2002; 43:509.]

[F-18] fluorodopa

For 9.0 mCi in a 70 kg adult H_E 0.60 rem bladder wall 5.1 rem
[Ref: Dhawan V, et al. J Nucl Med 1996; 37:1850-1852.]

[F-18] fluorothymidine

For 5.0 mCi in a 70 kg adult H_e 1.0 rem bladder wall 3.26 rem
[Ref: Vesselle H, et al. N Nucl Med 2003;1482-1488.]

C-11 methionine

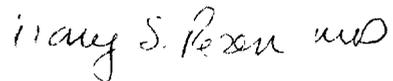
For 20 mCi in a 70 kg adult H_E 0.33 rem bladder wall 1.73 rem
[Ref: Deloar HN, et al. Eur J Nucl Med Mol Imag 1998; 25:629-633.]

Pediatric absorbed radiation doses are not available at this time for most PET radiopharmaceuticals, the exception being [F-18] 2-fluoro-2-deoxyglucose. In general, since both pediatric and adult calculated absorbed radiation doses are based on the same pharmacokinetic data, when pediatric administered activities are given on a weight basis, pediatric absorbed radiation doses are similar to those calculated for adults [See Stabin MG, Gelfand MJ. Q J Nucl Med 1998; 42:93-112 for many illustrative examples.]

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.

Thank you for the opportunity to comment on the proposed revision of the RDRC regulations.

Sincerely,

A handwritten signature in cursive script that reads "Nancy S. Rosen MD".

Nancy S. Rosen, M.D. F.A.C.R.
Co-Director Pediatric Radiology, Memorial Sloan-Kettering Cancer Center
Attending Radiologist, Memorial Sloan-Kettering Cancer Center
Professor of Clinical Radiology, Weill Medical College of Cornell University
1275 York Avenue, New York, NY
212-639-5511
rosen1@mskcc.org