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Division of Dockets Management  
HFA-305  
U. S. Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852

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

Dear Sir or Madam,

We are writing to you with regards to the potential modification of the Radioactive Drug Research Committee (RDRC) regulations. Obsolete radiological concepts and arbitrarily restrictive language in the current regulations severely limits the use of the RDRC regulations in the performance of radiopharmaceutical research in children. In particular, the current regulations severely limit the ability of researchers to apply new positron emission tomography (PET) and molecular imaging technology in the study of serious and often life-threatening diseases in children.

Research using radioactive drugs in children is essential. What we know about the physiology and metabolism of adults cannot be directly applied to children. It is important to realize that children are not just small adults. In fact, their metabolism and physiology can often vary substantially from that of an adult. In addition, the serious diseases that affect children are either often not encountered in adults or can be manifest in an entirely different manner. In the spectrum of pediatric cancer, only high-grade lymphomas frequently occur in both pediatric and adult populations. The other common pediatric tumors are infrequently encountered in adults. There is also a wide spectrum of pediatric congenital diseases that can significantly reduce life expectancy and cause significantly 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 studies correspond to adult nuclear medicine practice. Research using radioactive drugs is an essential approach for studying the metabolism and physiology in human populations. Therefore, it is essential that the current regulations be modified in such a manner as to allow the appropriate application of these methods in children.

The problems with the current RDRC regulations are threefold.

- The radiation absorbed dose limits are expressed in terms of whole-body dose. The current concept of "effective dose" as defined by the ICRP is more appropriate since this quantity is risk-based.
- The radiation absorbed dose to pediatric subjects is currently limited to 10% of adult dose. This arbitrary limit basically prohibits the use of new radiopharmaceutical techniques such as PET in the quest to better understand the metabolism and physiology

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of sick children. In the clinical application of nuclear medicine, the administered amount of the radioactive drug is scaled according to the patient's weight such that the pediatric patient receives essentially the same absorbed dose as the adult patient. Thus in many instances, the application of this 10% limit in pediatric subjects would reduce the administered amount to 10% of the amount necessary to appropriately perform the study, thus rendering the results as essentially useless.

- The limitation on target organ dose is inappropriate relative to the concept of effective dose. The use of effective dose essentially limits the risk associated with the irradiation of all organs without singling out that associated with a specific organ. Currently, there is an arbitrary limit of 0.5 rem (10% of 5 rem) to a single organ. 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. If it is deemed essential to have a target organ dose limit in addition to that inherent in the effective dose, it should be at least 10 times higher than the effective dose and not 1.6 times higher.

We also believe that the upper limit for effective dose 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 risk of exposure to a diagnostic radiotracer. An upper limit for 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 in these potential applications of critical importance.

Several additional issues have surfaced during the recent, public discussions of needed changes in the RDRC regulations that require clarification. The language in 21 CFR 361.1 (a), states 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 the biodistribution and kinetics in both normal and abnormal tissues. For example, one should be allowed to investigate the metabolism or receptor binding of a radioactive drug in both normal and malignant tissues. In the current regulations, this would be considered the study of both physiology and the pathophysiology. 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.

It has been argued by an FDA staff member that all studies in subjects under 18 years of age should be performed under an Investigational New Drug (IND) application rather than RDRC. 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. 21 CFR 50.53 permits "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" ... "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

## 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

Some examples of effective dose and target organ dose for selected PET radiopharmaceuticals are listed below. Pediatric absorbed radiation doses are not available for most PET radiopharmaceuticals except for  $^{18}\text{F}$  2-fluoro-2-deoxyglucose (FDG). However, since both pediatric and adult absorbed radiation doses are calculated based on the same pharmacokinetic data with the pediatric administered activities scaled by weight, the pediatric radiation doses will be similar to those calculated for adults.

Radiopharmaceutical	Effective Dose	Target Organ Dose
$^{18}\text{F}$ FDG in 70 kg adult (9.8 mCi)*	0.88 rem	6.8 rem
$^{18}\text{F}$ FDG in 10 year old (4.5 mCi)*	0.64 rem	3.6 rem
$^{18}\text{F}$ FDG in 5 year old (2.6 mCi)*	0.56 rem	3.6 rem
$^{18}\text{F}$ fluorocholesterol in 70 kg adult (7.7 mCi) <sup>#</sup>	1.0 rem	2.46 rem
$^{18}\text{F}$ fluorodopa in 70 kg adult (9 mCi) <sup>@</sup>	0.6 rem	5.1 rem
$^{18}\text{F}$ fluorothymidine in 70 kg adult <sup>†</sup>	1.0 rem	3.26 rem
$^{11}\text{C}$ methionine in 70 kg adult**	0.33 rem	1.73 rem

\*Ref: Stabin MG, Gelfand MJ. Q J Nucl Med 1998; 42:93-112.

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

@Ref: Dhawan V, et al. J Nucl Med 1996; 37:1850-1852.

†Ref: Vesselle H, et al. N Nucl Med 2003; 1482-1488.

\*\*Ref: Deloar HN, et al. Eur J Nucl Med Mol Imag 1998; 25:629-633.

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 may be 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 routinely experienced by these patients. 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.

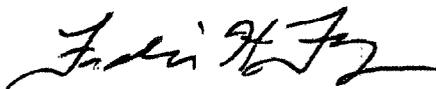
This returns us to our initial point of the benefits of research in pediatric subjects. Children and their families should be allowed to benefit from appropriately conducted research with diagnostic radiopharmaceuticals in sub-pharmacologic amounts under the RDRC regulations. We should strive to learn even more about the physiology and disease processes that can attack these most vulnerable and precious members of our society. The regulatory environment should not move in a direction that will make it more difficult to use of radioactive tracer technology. 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 medicine and imaging technology. 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 particularly those with cancer and other chronic life shortening, debilitating or life threatening diseases.

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

Sincerely,



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Frederic H. Fahey, D.Sc.  
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