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 Radioactive Drug Research Committee (RDRC) #0038, located at Lawrence Berkeley National Laboratory. 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) Radiation Dose Limits for Adult Subjects

The present dose limits that are defined in 21CFR361.1 are over 30 years old. There have been considerable changes in our understanding of dosimetry and in our knowledge base relative to the effects of radiation exposure. Given these changes, we support the conversion from whole body dose to "Effective Dose" with the use of tissue weighting factors as recommended by the International Commission on Radiation Protection (ICRP) in ICRP Publication 60 (1990). While the current annual whole body dose limit of 5 rem was based on the occupational exposure limit, this level remains appropriate for today's studies. Therefore, we recommend keeping the current whole body dose limit of 5 rem Effective Dose per year. Additionally, 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.

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

2) RDRC Membership

The FDA has raised the question of the benefit to the RDRC by the addition of individuals with expertise in pharmacology and/or toxicology. Given that the RDRC regulations do not permit first in human studies and that adequate pharmacology and toxicology 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 or toxicologist 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.

3) Children in RDRC Protocols

The federal Common Rule for human subjects research (45 CFR 26) allows greater than minimal risk research involving children when the study would either benefit the child directly, or if the study may yield generalizable information which might help understand, diagnose, or treat a condition suffered by children. This RDRC favors the adoption of language consistent with 45 CFR 26.406 to allow RDRC-monitored studies in children when the study is intended to study the subject's disorder or condition. The federal government, including the National Institutes of Health, has in recent years been promoting, even requiring, that research on applicable physiological and disease processes be conducted in children as well as adults. While the new proposal for Exploratory Investigational New Drug (E-IND) applications does not preclude studies in children, neither does it lay out any kind of framework for conducting such research. This open-ended process might better be reserved for studies involving compounds or methodologies which have no history of human testing. With amendment, the RDRC regulations would provide an appropriate framework for basic research studies in minors using radiotracers with some effective history.

We also suggest consideration of two additional modifications to the regulations to ensure adequate oversight for these studies. First, the regulation could require the addition of a pediatric consultant or member for any studies involving minors. Secondly, the regulation could specifically direct the RDRC to consider the risks inherent in any proposed anesthesia. The regulations should continue to require an immediate report to the Food and Drug Administration upon the approval of any pediatric study.

Lastly, the current restriction on radiation dose to 1/10 of that allowed for adult subjects is not science based, may encourage the use of anesthesia in order to permit longer scans, and generally precludes RDRC studies in children. We support an appropriately revised approach to limiting radiation exposure to minors.

4) Consent of Incapacitated Human Subjects

In section 361.1(d)(5) the current RDRC regulations require that subjects "…be at least 18 years of age and legally competent." This appears to preclude the use of the RDRC to review studies in subjects with mild to moderate dementia, or those who may become temporarily unable to consent for themselves because of a disease or treatment process (e.g., anti-psychotic drug washout). This is particularly unfortunate given the aging of our population and the interest in and availability of new treatments for conditions such as Alzheimer's , Parkinson's, and depression which disproportionately affect the aged. This RDRC recommends amendment of the regulations to allow RDRC-monitored studies in subjects who cannot give consent when the study may yield generalizable information which might help understand, diagnose, or treat a condition suffered by the subject.

This amendment should include protections similar to those proposed above for minors, such as the addition of a consultant familiar with the proposed subject group and the requirement for immediate report to the Food and Drug Administration upon the approval of such studies. Competency assessments and consent/assent requirements should be consistent with the Common Rule and applicable state laws.

Respectfully submitted by the members of RDRC 0038 – Lawrence Berkeley National Laboratory

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