Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 2005D-0122: Draft Guidance Exploratory IND Studies

1) Footnote 9 on Page 5 needs to be clarified. It states "A radiolabeled candidate compound can be administered at doses that are known to have no pharmacologic effect in humans without an IND application in basic research studies, following the initial publication in the medical literature of a first in human experience with that radiolabeled compound."

This statement raises several issues. While this statement may appropriately apply to entirely new chemical entities, there are several cases where initial publication of first in human studies does not make sense for new radiolabeled compounds. For instance, according to this note carbon-11 labeled choline would not be allowed to be studied first in humans until an IND or exploratory IND were obtained. As choline is found naturally in the body, along with several other compounds that might be isotopically labeled, the incrementally small increase to the choline pool from carbon-11 choline would not pose a risk to the subject under study. Further the isotopic substitution of a fluorine-18 for a fluorine-19 in a compound that has been safely administered to humans should also be allowed to be studied without an IND application.

This statement also implies that literature accounts of first in human experience with a nonradioactive compound would not be valid for initiation of an RDRC application. If a compound has been safely administered to humans at doses greater than would be given for an imaging study, with the same exact radiolabeled compound, then this too should be permitted under the RDRC mechanism.

The data that would confer safe administration of a radiolabeled compound may not necessarily come from the medical literature. Data obtained from a Phase I IND application or even an exploratory IND would be suitable for initiating studies of a new radiochemical entity under the RDRC mechanism. This may not necessarily be published information. Additionally, information, prior to publication, from other institutions where the radiolabeled compound has been safely administered to human subjects should also be allowed as documentation to initiate imaging studies.

The following additions are suggested to clarify this footnote. "*A radiolabeled candidate compound can be administered at doses that are known to have no pharmacologic effect in humans without an IND application in basic research studies, following the initial publication in the medical literature,* ***data from another institution where imaging studies have been performed, Phase I study data, or exploratory***

IND data *of a first in human experience with that radiolabeled compound* ***or the same exact non-radiolabeled compound****.*"

2) Under the section entitled "Chemistry, Manufacturing, and Controls Information" on line 196 the guidance states: "Although, in each phase of a clinical investigational program, sufficient information should be submitted to ensure the proper identification, strength, quality, purity, and potency of the investigational candidate, the amount of information that will provide that assurance will vary with the phase of the investigation…." Will USP<823> be accepted as standard for the preparation of radiolabeled compounds? If so, this and other examples of acceptable assurance criteria should be cited in this section of the guidance.

3) The section entitled "Clinical studies of pharmacokinetics or imaging" needs further clarification.

a) The second sentence of the second paragraph that starts on line 318 states that a single species may be justified by "in vitro metabolism data and by comparative data on in vitro pharmacodynamic effects". It is not clear what these in vitro measures are. Examples of the in vitro studies being referred to here should be added to this section or this sentence should be clarified.

b) There appears to be some inconsistency between the definition of the microdose and the determination of minimal toxic effect or the margin of safety. Microdose as defined on line 310 is less then 1/100th of the dose calculated to yield a pharmacological effect and a maximum dose of ≤100 micrograms. On line 323 the guidance states "The study should be designed to establish a dose including a minimal toxic effect, or alternatively, establishing a margin of safety." If 100x the proposed human dose produces a minimal toxic effect than it does not meet the margin of safety criteria. On the other hand if the 100x dose does not produce a minimal toxic effect will the investigator need to demonstrate the minimally toxic dose?

c) The microdose definition refers to a pharmacological effect whereas the proposed preclinical studies refer to a toxicological effect. This section should be clarified to eliminate the interweaving of both of these effects.

d) The definition of microdose is given as "less than 1% of the dose calculated to yield a pharmacological effect of a test substance and a maximum of ≤ 100 micrograms". This definition, that parallels the European Medicines Agency (EMEA) position paper, references the maximum mass of the compound to be injected. Mass is not necessarily the best unit to use in this case as it is the number of moles of the compound (i.e. the number of molecules) that will dictate the pharmacological effect. As the molecular weight of test substances increases the number of moles decreases. Thus, we recommend that the maximum number of moles be specified rather then the mass. Given a minimum molecular weight of a test substance of 100 gper mole then 100 μg will be one μ mole, thus the maximum dose would then be 1 micromole.

Suggested revised microdose definition:

A microdose is defined as less than 1% of the dose calculated to yield a pharmacological effect of a test substance and a maximum of ***≤ 1 micromole***.

Respectfully submitted on behalf of the Society of Nuclear Medicine by

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