July 13, 2005

Division of Drug Information (HFD-240)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2005D-0122
Draft Guidance for Industry on Exploratory Investigational New Drugs Studies; Availability

Dear Sirs/Madams:

I would like to provide the Food and Drug Administration (FDA) with the following comments and suggestions regarding the FDA's *Draft Guidance for Industry on Exploratory Investigational New Drugs Studies*.

For your information, I am a certified nuclear pharmacist by the Board of Pharmaceutical Specialties), and a current member of the American Pharmacists Association (APhA) and the Society of Nuclear Medicine (SNM). My current employer is Mayo Clinic, where I serve as a Consultant and Director of Nuclear Pharmacy Laboratories and PET Radiochemistry Facility, as well as hold the academic positions of Professor of Pharmacy and Professor of Radiology, Mayo Clinic College of Medicine. I also serve as a member of the Radioactive Drug Research Committee (RDRC) at Mayo Clinic – Rochester, MN.

Please note that my personal comments and suggestions as stated below does not necessarily represent the viewpoints of the APhA, SNM, or Mayo Clinic.

Definition of "Microdose"

As per lines 310-311 of the FDA's *Draft Guidance for Industry on Exploratory Investigational New Drugs (IND) Studies*, the term "microdose" is defined as (in bold, underlined print for emphasis) "less than 1/100th of the dose calculated to yield a **pharmacological effect** of a test substance and a maximum dose of <100 micrograms."[15] The above definition is literally identical to the one as stated in FDA's cited reference #15 (see below)

[15] See European Medicines Agency (EMEA), Evaluation of Medicines for Human Use, "Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose," CPMP/SWP/2599/02Rev 1, 23 June 2004.

The aforementioned statement seems to indicate that the "microdose" concept is applicable only to a **pharmacologically active** compound, rather than to a compound that does not cause any clinically detectable pharmacological effect in human subjects.

Sub-pharmacologic or Non-pharmacologic Radiotracers

As sub-pharmacologic or non-pharmacologic radiotracers are the most commonly used agents in the field of nuclear medicine, the aforementioned "microdose" concept would not be applicable to these radiotracers. If a radiotracer is not anticipated to cause any pharmacological effect in human beings, the amount of the aforementioned compound to be utilized in a microdose study would be zero (i.e., 0 pharmacological dose ÷ 100 = 0 microdose).

The reason that we do not wish to use any pharmacologically active compounds in nuclear medicine practice is that the principle for clinical usage of a radiotracer is based <u>not</u> upon its ability to produce a pharmacological effect, but rather on its capability to differentiate between normal and abnormal physiological processes, as evidenced by altered distribution patterns and different pharmacokinetics of the agent. In fact, the production of pharmacological or physiological effects by a radiotracer is undesirable, since the agent should not modify the parameter it is attempting to measure.

Pharmacology or Toxicology Information

The intention of the second paragraph (lines 317-332) is to address issues related to the design and performance of non-clinical toxicity studies in order to establish a "margin of safety" to allow clinical trails using microdose technique to be studied "first in humans" in a safe manner. As such, the main objective of the non-clinical safety studies is to evaluate any potential toxicological (or adverse effects), rather than to gather pharmacological, information of the radiotracer. Please refer to the excerpts below (in bold, underlined print for emphasis) to substantiate the aforementioned case in point:

- Line 317 … the use of extended, single-dose **<u>toxicity</u>** studies …
- Line 324 a dose inducing a minimal **<u>toxic</u>** effect, …
- Line 326 … does not induce **<u>adverse effects</u>** in the experimental animals.

The placement of non-clinical toxicity studies (i.e., lines 317-332) within a section titled "*Clinical studies of pharmacokinetics or imaging*" which specifically refers to clinical studies using microdose techniques is inadequate and confusing. The FDA should include a separate section in the draft guidance or develop a new guidance similar to the "Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose" as published by the EMEA (see FDA's cited reference #15).

Extended, Single-Dose Toxicity Study

There are some valid recommendations from EMEA (see FDA's cited reference #15) with regard to the design of an extended, single-dose toxicity study. I would like to suggest that the FDA consider inclusion of the following items in the guidance:

- The extended single-dose toxicity study should include a control group.

- The number of animals in either the control or treatment group should be sufficient to ensure reliable interpretation of the study results; however, the number of animals to be studied should be kept as minimal as possible with the intention to obtain the maximum amount of information.
- Inclusion of both genders should be considered.

A Proposed Evaluation Pathway for New Radiotracers

As per the aforementioned discussion, it seems that an exploratory IND approach using the microdose concept may not be applicable to a sub-pharmacologic or non-pharmacologic radiotracer. Although the aforementioned agent would be suitable for RDRC evaluation, confirmation that radiotracer of interest would not cause any human pharmacological effect is a challenging issue to overcome.

I would like to take this opportunity to propose an evaluation pathway (see below) for a new radiotracer in order to allow investigator(s) or sponsor(s) to move their new radiotracer more efficiently during R&D and regulatory review/approval processes, and at the same time maintain the needed protections for general public.

Non-Clinical Pharmacological Assessment

To determine whether the new radiotracer would have human pharmacological effect in human beings, a single mammalian species (the treatment group should consist of an adequate number of animals, and the use of both genders should be considered) can be administered with the proposed human dose that is scaled back based on body surface difference between humans and animals. The route of administration in animals should be the intended clinical route.

If there is any noticeable pharmacological effect observed in animal(s) of the treatment group in comparison with the animals of the control group, the radiotracer will then be evaluated under the section titled "***Pharmacologically Active Radiotracers***".

If there is no detectable pharmacological effect found in all animals of the treatment group, the radiotracer will then be studied under the section titled "***Sub-Pharmacologic or Non-Pharmacologic Radiotracers***".

Pharmacologically Active Radiotracers

Non-Clinical Toxicity Study

A single mammalian species (the treatment group should consist of an adequate number of animals, and the use of both genders should be considered) is administered with a large multiple (e.g., 100X) of the proposed human dose of the new radiotracer via the intended clinical route of administration. Please refer to lines 317-328 of the draft guideline, as well as a section titled "Recommendations" of the FDA's cited reference #15 for further information with regard to the design and performance of the non-clinical toxicity study.

If the administered dose (i.e., 100X of the proposed human dose) produces adverse effects in the experimental animals, the proposed human dose should be scaled back accordingly and the above evaluation should then be repeated with 100X of the reduced human dose of the radiotracer.

First in Human Clinical Trial Using a Single Microdose Technique

A limited number of human subjects are studied under the exploratory IND process with the single microdose technique. Basically each of the participating human subjects is administered with a single microdose of the new radiotracer. The term "microdose" is defined as "less than $1/100^{th}$ of the dose calculated to yield a pharmacological effect of a test substance with a maximum dose of ≤1 micromole".

Sub-Pharmacological or Non-pharmacologic Radiotracers

Non-Clinical Safety Study

A single mammalian species (the treatment group should consist of an adequate number of animals, and the use of both genders should be considered) is administered with a large multiple (e.g., 100X) of the proposed human dose of the new radiotracer via the intended clinical route of administration. If the administered dose of 100X proposed human dose produces pharmacological or adverse effects in the experimental animals, the proposed human dose should be scaled back accordingly and the above evaluation should then be repeated with 100X of the reduced human dose of the radiotracer.

Pre-RDRC First in Human Clinical Trial

Differing pharmacological responses to the new radiotracer may be observed between animal and human (i.e., radiotracer may not induce a pharmacological effect in experimental animals, but may cause a pharmacological effect in human beings). Thus, a limited number of human subjects will be studied initially with less than $1/100^{th}$ of the proposed human dose (with a maximum dose of ≤1 micromole) of the radiotracer of interest. If there is no human pharmacological effect noted in the aforementioned human subjects, another group comprised of a limited number of human subjects will then be administered with the proposed human dose of the new radiotracer. If the radiotracer of interest still fails to cause any clinically detectable pharmacological effect in the participating human subjects, the evaluation process for the new radiotracer will then be moved to the RDRC phase.

RDRC

Please refer to 21 CFR Part 361 for the conditions set forth for a new radiotracer to be studied under RDRC rules.

Many thanks for the opportunity that the Agency has provided to allow me to offer my concerns and comments with regard to the FDA's *Draft Guidance for Industry on Exploratory Investigational New Drugs Studies*. If you have any questions or need additional information regarding my comments and suggestions, please do not hesitate to contact me by phone: (507)284-4399, fax: (507) 266-4461, or e-mail: jhung@mayo.edu.

Respectfully submitted,

Joseph C. Hung, Ph.D., BCNP