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Lexington KY 40502-3201  
July 08, 2005

Division of Documents Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville MD 20852

Attn: Docket No. 2005D-0122

Gentlemen:

Here are my comments – submitted as an individual – on the draft guidance entitled “Exploratory IND Studies”. I have practiced nuclear pharmacy at a VA Medical Center and at commercial nuclear pharmacies in the state of Kentucky.

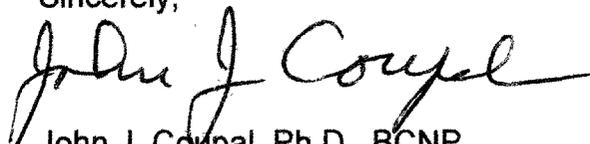
I currently serve as Chair of the University of Kentucky Radioactive Drug Research Committee (0151). These comments and questions are my own and do not necessarily reflect those of the University of Kentucky or of its RDRC members.

Comments on that draft guidance also will be submitted separately by the University of Kentucky, Lexington, KY.

If there are any questions, I may be reached by telephone at (859) 277-2596 or e-mail at: [jcoupal@qx.net](mailto:jcoupal@qx.net).

Thank you for your consideration!

Sincerely,



John J. Coupal, Ph.D., BCNP  
Nuclear Pharmacist

Enc.: Comments on Draft Guidance “Exploratory IND Studies”  
Certified Mail 7002 3150 0001 7119 5613  
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2005D-0122

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**Docket No. 2005D-0122**

**Comments to Draft "Exploratory IND Studies"**

**G:\6384dft.doc dated 04-07-05**

**Submitted by John J. Coupal, Ph.D., BCNP, Page 1, July 08, 2005**

**Specific Comments**

My comments and questions appear under appropriate page and line numbers appearing in the FDA pdf Draft. My comments and questions appear in brackets. Direct quotes of Draft text appear within quotation marks.

Page 1 - Line 32 to Page 2 - Line 39

[An exploratory IND study on a potential diagnostic radiopharmaceutical would not appear to necessitate the following traditional dose escalation, safety, and tolerance studies due to minimal risk from the drug substance to human subjects. FDA should waive requirement for those subsequent studies given the clinical benefit and low risk of the drug product to humans.]

Page 2, Footnote 2 to line 76: [Does this guidance apply to diagnostic radiopharmaceutical drugs which are characterized by low quantity of dose (both in units of mass and radioactivity), infrequent dosing, and absence of pharmacologic effect?]

Page 3 - Lines 103, 104, and 107:

[Since those examples of applications apply to diagnostic radiopharmaceuticals, does FDA consider Exploratory IND Studies an appropriate route for radiopharmaceutical manufacturers (sponsors) to take when initiating studies and regulatory filings on non-therapeutic radiotracer drug substances intended to lead to an NDA?]

Page 5 - Lines 181-185 plus Footnote 9

[If a sponsor were to employ a sub-therapeutic dose of a diagnostic radiopharmaceutical in an exploratory IND study (a clinical trial), could an IRB and RDRC approve that study? Current FDA regulations do not allow approval of a clinical trial by an RDRC. If a sponsor were to plan to administer a sub-therapeutic dose of a diagnostic radiopharmaceutical to humans in an exploratory IND study, would that study be considered a phase 1 clinical trial acceptable to the FDA? If so, the FDA should increase the number of experimental subjects and controls required under such a scenario.]

Page 9 - Lines 310-315:

[The microdose concept comes from the European Medicines Evaluation Agency (EMEA). It is defined as 1/100<sup>th</sup> of the dose calculated to yield a pharmacologic effect of a test substance and a maximum dose of  $\leq 100$   $\mu$ g. The European Community (EC) has used a "Precautionary Principle" in

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regulatory decision-making for evaluating new medicines, chemicals, and other items being considered for approval for marketing within the EC. However, the public and private sectors of the United States have not usually adopted that Principle. For such new products, our public and private sectors judge the Principle to be too conservative in its basic assumptions: it designates a new entity to be dangerous (until it is proven not to be) and it is too burdensome in its implementation.

- a. What is the scientific evidence supporting the FDA's choice of 1% of the pharmacologic dose for an exploratory IND study? FDA should ensure that such evidence is acceptable to current American scientific and clinical judgement on its applicability?
- b. What is the scientific evidence supporting the FDA's choice of 100 µg as the maximum dose? FDA should ensure that such evidence is acceptable to current American scientific and clinical judgement on its applicability?
- c. There are many FDA-approved diagnostic radiopharmaceuticals (e.g., Tc-99m- or In-111-labeled products) that may be injected intravenously into patients in which the radionuclide-ligand dose complex (or radionuclide-bound protein or peptide dose) weighs more than 100 µg, and yet has neither pharmacologic nor toxic effect. An arbitrary upper limit of 100 µg would necessarily exclude such drug substances from exploratory IND studies and risk failure to study such an effective diagnostic radiopharmaceutical drug substance.]

Page 9 - Line 320:

[A word appears to be missing]

“..pharmacodynamic effects. The route of exposure in animals should be [by] the intended clinical..”

Page 12 – Lines 436-438:

“This is because for the approaches discussed in this guidance, which involve administering sub-therapeutic doses of a candidate product or products, the potential risks to human subjects are less than for a traditional phase 1 study.” [A diagnostic radiopharmaceutical in routine clinical use holding an approved NDA is administered to humans in a sub-therapeutic dose. however, that would also be the case for preclinical/early clinical testing of that same drug substance. Therefore, it appears that this exploratory IND concept should be applied to diagnostic radiopharmaceuticals in order to speed the data acquisition on drug substance safety/efficacy studies and FDA evaluation thereof.]

### **General Comments**

The concept of “Exploratory IND Studies” is excellent. FDA intends it to speed preclinical/early clinical study of drugs providing benefit and posing minimal risk to humans.

Implementing that strategy allows early identification of ineffective drug entities, allowing them to be eliminated from further consideration and testing (*i.e.*, “forcing them to fail early”, thereby reducing time and expenditure undergoing further studies). The FDA's consideration of this new approach to simplify IND submissions - when warranted - is commendable. That should reduce costs to pharmaceutical researchers and manufacturers and speed access to market of safe and effective drugs.