

GE Healthcare

September 15, 2005

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Documents Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0223
Comments to Draft Guidance – Nonclinical Evaluation of Late Radiation Toxicity

Dear Documents Management Staff:

Reference is made to the subject docket number published in the Federal Register Volume 70, Number 117, page 35448 which announced the availability of a draft Guidance for Industry, Investigators and Reviewers entitled "Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals."

At this time, as requested by the Federal Register notice, GE Healthcare is providing its comments to the draft guidance on the following page.

Please call me at (609)-514-6573 if you have any questions or comments regarding this submission.

Sincerely,
GE Healthcare



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Director, Regulatory Development

2005D-0223

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Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies – Draft Guidance – June 2005

(Docket No. 2005D-0223)

GE Healthcare Comments

Lines 65-70 – The draft guidance states: "Available radiation dosimetry software programs (e.g., Medical Internal Radiation Dose (MIRDOSE) and Organ Level Internal Dose Assessment (OLINDA)) can be used to provide only rough estimates of radiation absorbed doses received by specific organs following administration of therapeutic pharmaceuticals. The accuracy of such estimates is determined by the accuracy of the pharmacokinetic data that are used in the model."

It is GE Healthcare understanding that only OLINDA has 510(k) clearance. Its documentation package (18 November 2004) states that: "(the) doses estimated by this code should not be used to evaluate risk to an individual patient, as the risk weighting factors are meant to be applied to population averages. The number most certainly should not be used in situations involving radiation therapy, as non-stochastic effects are more important ". Moreover, the accuracy is not limited solely by that of the pharmacokinetic input data. OLINDA does not explicitly include the effects of radioactive daughters, which will be an important issue with alpha-emitting isotopes. The accuracy is also limited by how closely the individual approximates the 70 kg hermaphrodite phantom or other phantoms used in the OLINDA code.

GE Healthcare is concerned that the draft guidance document is suggesting the use of software (MIRDOSE) for radiotherapy purposes that ended its distribution in 1999 / 2000 by Oak Ridge National Laboratory because users were using the code for that purpose and the use of software (OLINDA) for radiotherapy purposes when the code's documentation explicitly states that the code should not be used for that purpose.

Line 187-189 – GE Healthcare questions whether it is necessary to perform late radiation toxicity studies for all therapeutic agents based on a particular radionuclide. Since the effect will be dependent on a combination of the pharmacokinetic and physical characteristics of the nuclide (half life, energy, LET, etc) it is to be expected that a good understanding of the changes in the pharmacokinetics (and drug disposition) of a drug labeled with a particular nuclide would be reasonably predictive of late radiation effects. Consequently, it would not be necessary to perform a long term study if appropriate pharmacokinetic and distribution data were available?

Lines 193-196 – If a pharmacokinetic / biodistribution is acceptable to address the subject of late radiation effects must it be a GLP study (see the preceding comment to line 187-189)? Ordinarily these types of studies are not required to be GLP studies.

Line 214 – Does the term “tracer doses” refer to (1) small chemical doses of intended “normal” specific activity or (2) “normal” chemical doses of low specific activity? GE Healthcare believes that the latter makes more sense if the Agency is proposing a study to reduce the risk of late events whilst collecting appropriate pharmacokinetic / distribution data.

Lines 232-234 – The guidance states that preclinical studies should: "mimic the design of the anticipated clinical studies including the injected amount of radioactivity (mCi/m²), number of doses, frequency of dosing, and dosing interval."

This is based on a classical toxicology study design but GE questions whether this is appropriate in this situation where the effects will be due to the radiation dose absorbed by particular radiation sensitive organs and tissues. The nature and extent of any effect will be related to both the cumulative radiation dose and also to the radiation dose rate. So a cumulated dose which has been fractionated (as in the suggested design might be expected to have a very different outcome to the same cumulative dose achieved from a single dose of radioactivity). There is little published evidence to suggest that it is possible to directly extrapolate the effects of a fractionated radiation dose from rodents to man.

We would suggest that whilst the approach may be valid the guideline wording is probably too specific. We would suggest an alternative wording such as:

"The design of preclinical studies to investigate the potential for late radiation toxicity effects should take into account the design of the anticipated clinical studies including the injected amount of radioactivity (mCi/m²), number of doses, frequency of dosing, and dosing interval but also such factors the relative tissue turnover rates and the relative biodistribution/pharmacokinetics in the test species and man."

Lines 287-290 – GE Healthcare requests clarification of the wording in the last part of this sentence. The current wording could be interpreted to mean that a sponsor should compare the results from the radiopharmaceutical with results from external beam treatment which we do not believe is the intention of this sentence. We do not believe that is necessary to perform comparative studies with external beam treatment.

Lines 296-300 – The draft guidance states: "Since pharmacokinetic parameters for some of these agents have been known to vary significantly from patient to patient, before any patient is treated, biodistribution and pharmacokinetic data should be obtained for that individual patient using quantitative gamma camera imaging with diagnostic doses of the therapeutic agent where possible."

This is not always a convenient arrangement in that in order to image with a gamma camera, one requires gamma rays and there is an emphasis upon radiotherapeutics using particulate (alpha- and beta-emitters) with short range. In principle, beta-emitters have been imaged indirectly through bremsstrahlung radiation, but this requires a therapeutic rather than diagnostic level of activity.

Lines 300-302 – The draft guidance states: "These data should be used to estimate radiation absorbed doses to each individual patient's critical organs using MIRDOSE-3 or OLINDA (or other adequate) dosimetry software."

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Lines 301-302 – Please verify that the two software packages listed are equally acceptable to the Agency. What guidance can the Agency give for determining that other software is "adequate"?