

October 26, 2004

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

Re: Docket No. 1998D-0785: Guidance for Industry: Developing Medical Imaging Drug and Biological Products (June 2004)

Dear Sir or Madam:

Thank you for the opportunity to comment on the revised guidance for industry entitled "Developing Medical Imaging Drug and Biological Products". GE Healthcare would like to provide the following comments (which are grouped according to the pertinent part of the three-part guidance):

Part 1: Conducting Safety Assessments

General: There are a number of instances throughout the document where it seems that "radiation dose" has been used when it should be "radioactive dose".

Lines 113 - 115: This sentence refers to "radiation absorbed dose" as a characteristic of medical imaging agents that can lead to a more focused safety evaluation. However, there is no further mention of this characteristic.

Lines 122 - 124: No definition of what is a dose-response curve is given.

Lines 145 - 148: There is still no clarification of what is regarded as "infrequently or as single doses" and what is regarded as "repeatedly (e.g. to monitor disease progression)". This distinction is important for determining what sort of repeat-dose studies should be done. What time interval between single doses is necessary for a change from "repeatedly" to "infrequently"?

Line 231: Below Table 1 there is a footnote (c) which does not appear in the Table itself.

Line 262: Change "reducing drugs" to "reducing agents".

Line 325: Does the definition of biological include or exclude peptides regardless of whether they are from natural or synthetic sources?



Lines 436 – 438: How should we interpret the word “identical” here? During development there may be changes to both the formulation and reconstitution procedure.

Lines 476 – 481: This statement is confusing as there will be radiopharmaceuticals for which analytical methodology may not allow for the detection of the ligand; thus, “true” pharmacokinetic information cannot be obtained even though the radioactivity can be monitored.

Lines 540 – 542: The MIRD phantoms do not represent the average patient but the average male, average female, average pregnant female, etc. Following this statement is a list of four quantities (organs/tissues accumulating significant activity, the amount of activity accumulated, the times at which these were measured and the time-integral) that are claimed to be derivable from the MIRD phantom. They are not derived from the phantom but are derived from *in vivo* measurement of activity in subjects. The MIRD phantom is used solely to calculate organ absorbed doses to a reference man, woman, etc.

Lines 546 – 547: This is a recommendation for the presentation of the amount of activity in the above organ(s) to be expressed as a percentage of the administered activity. But the recommendation doesn't specify if these are at several time points during cumulation and washout or at the time where the activity content is at a maximum. The statement needs considerable firming up.

Lines 558 – 561: The term "time-integral" should be avoided. Its proper use would be as the "time-integral of [something]" - but [something] is never stated in these recommendations. It would be better to use the correct term "cumulated activity".

Lines 587 – 588: Does the statement “potential radionuclide contaminants that may be present in the product” refer to radionuclidic impurities only? What about the situation if these impurities are not isotopes of the intended radionuclide? Also, there seems to be no mention of potential radiochemical impurities.

Lines 616 – 618: The calculation of the organ absorbed dose resulting from a diagnostic x-ray procedure is next-to-impossible to do accurately without very involved methods (e.g., Monte Carlo). It also requires detailed information regarding the imaging protocol used, collimation of the x-ray beam, exact patient positioning, etc - information rarely available at hand. Rather than state that the radiation absorbed dose be calculated, it would be best to recommend that it be estimated from published data or at least an upper limit established.

Lines 619 – 621: We suggest deleting “and as rad per millicurie (mCi)”. There is no reason to specify the unit of mGy; the unit of μGy is actually better to use (e.g., 7.1 $\mu\text{Gy}/\text{MBq}$ is easier to use than 0.0071 mGy/MBq and less prone to transcription error).

Lines 623 - 624: The section on Radiation Safety Assessment concludes with “...be presented in a tabular format and include the individual radiation absorbed doses for the target tissues or organs listed and the organs listed above in section IV.D.1. Not only is

there no section IV.D (because section IV.C in the previous draft version has been deleted) but specific organs are no longer specified in what is now IV.C.1.

Lines 628 – 631: This definition of the effective dose is incorrect. This definition states that *all* organs contribute to the effective dose; this is not true. Only a small number of organs or tissues are accounted for in this calculation. Also, what is “R” in the expression?

Lines 636 – 640: The Glossary contains a definition for NOAEL which is not consistent with the definitions given in Footnote 18. Also, it contains a definition for NOEL which is not even mentioned in the text.

Lines 661 – 664: The Glossary also refers to “standard acute toxicity study” which is not mentioned in the body of the text.

Part 2: Clinical Indications

Line 87: Change “atom” to “molecule”.

Line 368: Change “predictable” to “predictive”.

Lines 393 – 397: What is meant by measurement? Is an image a measurement or does this imply quantification in all cases?

Part 3: Design, Analysis, and Interpretation of Clinical Studies

Lines 110-112: How should we interpret this? Could this be evaluated preclinically and then justify not having to confirm in clinical trials?

Lines 116 – 120: When does something become a “large” amount?

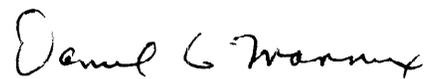
Lines 370 – 372: Does the active/inactive here imply something to do with retained “biological” activity? If not what does it mean?

Lines 717 – 719: Does this imply two separate independent panels reviewing the two datasets? If so, does this not introduce potential bias due to the relative experience of different panels with old and new agents?

Line 864: Will the agency accept an argument that it is not ethical to do this sort of comparison between two radioactive drugs on the basis of an unacceptable radiation burden resulting from the use of both agents?

If you have any questions concerning these comments, please contact me at 609-514-6494.

Sincerely yours,

A handwritten signature in black ink that reads "Daniel G. Mannix". The signature is written in a cursive style with a large initial 'D'.

Daniel G. Mannix, Ph.D.
Vice President, Regulatory Affairs

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