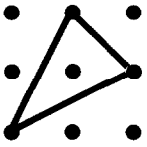

Amersham Health

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June 17, 2003

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

RE: DOCKET NO. 98D-0785

Dear Sir or Madame:

Thank you for the opportunity to comment on the revised draft guidance for industry entitled "Developing Medical Imaging Drugs and Biological Products". Amersham Health would like to provide the following comments:

Part 1 - Conducting Safety Assessments

Footnote 6 - It is unclear what is meant when referring to an imaging agent "not possessing any special characteristics". Each product is unique and would thus have its own special characteristics.

Line 145 - We would like to see some more clarification regarding these aspects. Does the agency consider it a different situation when a product is given every 6 months to monitor therapy compared to treatment twice a week? How will this reflect in the duration of the repeat dose studies? Is the agency thinking about repeat dose studies longer than 14 days?

Line 151 - It would be interesting to have an idea about what kind of endpoints the agency would want to be included in such a clinical study.

Lines 198 - 199 - We prefer that it should be stated that carcinogenicity studies are normally not needed, instead of formally asking for a waiver.

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Line 217 - Table 1 - Recently the CPMP has issued a position paper on non-clinical safety studies to support clinical trials with a single microdose. The microdose is defined as $1/100^{th}$ of the dose calculated to yield a pharmacological effect and this is typically below the 100 microgram/person scale. The recommended studies are:
- a study in rats
- a CV study in dogs
- two genotoxicity studies
- limited metabolism studies

It would be useful if the agency can comment if such an approach is feasible in the US and what kind of studies should be included

Line 217 - Table 1 - Under local tolerance it is specified that blood compatibility and protein flocculation studies should be performed. However, we would like to suggest that these studies are performed only if there is a suspicion of some type of interaction.

Line 217 - Table 1 - Which test as mentioned in the ICH S7B guideline should preferably be performed in relation to the different clinical phases?

Line 217 - Table 1 - What is the value of performing an expanded single dose study before Phase 2 if data from a short term repeat-dose toxicity study and a non-expanded single dose study are submitted prior to Phase 1?

Line 217 - Table 1 - Is the preferred duration of the short term repeat-dose toxicity study 14 days?

Line 233 - It would be helpful if it can be specified that long-term repeat dose studies are probably studies longer than 14-days repeat dose studies.

Line 251 - Can it be assumed that "evaluation of all components in the final formulation for toxicity" can be covered by known (published) data including use at similar (or lower) levels in drug formulations administered at same (or lower) dose and/or determination of a component as being GRAS?

Line 306 - Clarification is needed on what is a biologic product. A definition is given in Footnote 14, but it is not all encompassing. For example, are synthetic peptides biological products?

Line 322 - Most radiopharmaceuticals go to the liver and kidney. Does this mean that we specifically must look at this in every case?

Footnote 16 - Clarification is needed on the term biologically inactive. Can this include ligands and carriers that might be targeted/bind to receptors and transporters?

Lines 345-346 - This section requires duration of monitoring beyond what would be predicted based upon what is known about the drug (including PK). Such a statement requires an unstated duration beyond what would be reasonable and logical based upon

the existing data. What logical guidance can FDA provide in setting this duration? How far into development would such an extended monitoring be expected (Phase 2) if no signals are seen?

Line 367 onwards - Clarification is needed on the safety limit of "at least one hundred-times greater". Does this apply only to the main peak, or to all components? What defines a valid test article in terms of levels of impurities?

Line 428 - It would be helpful if there is a reference to the paper about the good practice guidelines for administration of volumes of test items to animals (i.e., *Diehl et al. A good practice guide to the administration of substances and removal of blood, including routes and volumes. J Appl Toxicol. 2001 Jan-Feb;21(1):15-23*)

Line 446 - It is illogical that an agent not be able to qualify for Group 1 designation based upon a single adverse event occurring at any time during human studies. Such a designation should be determined on the available non-clinical and clinical safety data in total.

Line 451 - FDA should clarify whether the proposed human pharmacokinetic studies pertain to the ligand itself or the labeled radiopharmaceutical. Also, is it implied that this data is needed when results of non-clinical studies meet all recommended safety criteria?

Line 483 - In the list of organs and tissues to be included in dosimetry estimates, the exclusion of breast is surprising.

Line 513 - How does the agency define an "average patient"?

Line 548 - Replace the word "decay" with "impurities".

Line 553 - There is the recommendation that doses be expressed at gray (Gy) per MBq or per mCi. We recommend that doses are expressed as Gy per MBq, which is the standard international unit. The term Gy per mCi is quite unusual.

Part 2 - Clinical Indications

Line 111 - Include a reference to Section IV. B. at the words "clinical useful information". Also, we recommend that this phrase be changed to "valid, clinically useful information

Lines 166 -168 - This statement implies that there is a gray zone between structure (i.e., in the case of abnormal anatomy) and disease detection indications. The agency should better clarify what constitutes a structure indication and what constitutes a disease detection indication. We would also propose that these lines to revised to state:

> In the preceding examples, the agent's ability to outline abnormal anatomy might also support a disease detection indication (Section III.B.). If that is the use

intended by the sponsor, a disease detection indication should be sought. However, that does not preclude an indication to outline abnormal anatomy if that is preferred by the sponsor.

Lines 192 - 193 - What guidance can the agency provide in defining the terms "high enough" and "low enough"?

Lines 229-230 and Glossary line 636 - A general source of discussion within the industry has been the distinction between comparator and reference / truth standard. Some use the word "reference" as a synonym to "comparator" whereas some use it as a synonym for "truth standard". It appears that FDA use reference and truth standard interchangeably. To ensure clarity, the word "reference standard" should be added to the glossary. The term "comparator" should also be defined in the glossary.

Lines 233 – 234 – Please clarify what is meant by "the wide spectrum of diseases and disease severity states" and what effect this would have on the number of studies required to support approval of an agent seeking a functional, physiological, or biochemical assessment indication.

Line 264 - Why the word "irreversible" used here? Surely any reduction in morbidity (even if transient) is beneficial to the patient.

Line 295 onwards – Amersham Health supports the FDA view that the clinical usefulness of imaging agents used for structural delineation, detection of disease or pathology, or assessment of some functional, physiological, or biochemical parameter is generally well-established and should not have to be demonstrated directly during clinical development. This represents a positive change from the FDA view taken in the June 2000 version of this draft guidance.

Line 338 - 341 - The statement is made that an imaging agent should be studied in subjects over the full spectrum of a disease and in those presenting with other diseases or conditions that could affect image interpretation. It would be valuable if the agency clarified what this meant in terms of number of required studies and how this would affect statistical planning.

Line 361 onward - the information in this section to contain a footnote that that certain exceptions may apply. Specifically, a product should be judged by virtue of establishing confidence in diagnosis of the disease at any stage (symptomatic and non-symptomatic), not necessarily in the effectiveness of patient management measures, unless that is the type of indication a sponsor is seeking.

Also, we would also like the following point be added: In the presence of an already validated measure of effectiveness for one product, it is no longer necessary to prove clinical usefulness in the case of a second product under investigation.

We suggest that if an agent under investigation provides diagnostic information that is substantially equivalent to information obtainable from a diagnostic test that is already used clinically, then the clinical usefulness of the information would be deemed to have been established. For example, suppose a new diagnostic agent detects thrombi. The fact that at least one test already exists and is used clinically to determine whether or not a patient has thrombi would be sufficient to establish the clinical usefulness of the new test. Acceptable evidence that an existing test provides substantially the same information as an investigational test would include literature reports, professional society guidelines, and other sources.

Line 391 - The phrase "early detection of colon polyps" may be more accurate than the existing phrase "diagnosis of early colonic polyps."

Lines 522 - 523 - Why is it necessary that the published article have an extensive discussion if there is an extensive discussion of the overall data in the sponsor's review? We suggest that this recommendation be deleted as it is unnecessary and may lead to omission of appropriate literature.

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

Line 104 - Please replace the phrase "human toxicology assessments of the safety of a single dose" with "human safety assessments of a single dose".

Line 105 - It is not clear whether FDA means mass dose, radioactive dose or both. This should be clarified.

Line 113 - In the phrase "when large amounts of cold components are present", it is unclear what is considered "large". Is it determined by absolute measurement or is it determined by relative concentration labelled to unlabelled ligand / carrier?

Lines 237 – 239 – FDA recommends that sponsors submit a comprehensive statistical analysis plan (SAP) for each principal efficacy study as part of the study protocol. Does FDA mean a detailed statistical methods section in the protocol or a detailed SAP document? We do not submit formal SAPs to the FDA, as they are typically not even approved internally until several months after the protocol has been submitted.

Lines 260 – 262 - This seems to imply that a baseline image should be performed. Why is this being suggested?

Lines 396 – 398 – When is one type of blinded read recommended over the other?

Line 439 – Can examples be given?

Line 543 - Is the restriction on consensus evaluations intended to prevent use of such for the truth standard? If so why? In either case please make this clear. A similar question

arise for section IV-B-10) on page 16 regarding use of multiple readers. Does this same restriction apply to the truth standard read? Please explain and clarify.

Lines 614 - 615 - The sentence implies that assessment of inter-reader variability be done at some point during development. Is it sufficient to do this only during Phase 2?

Lines 652 – 653 – This section should also address the situation when images obtained with the gold standard are missing.

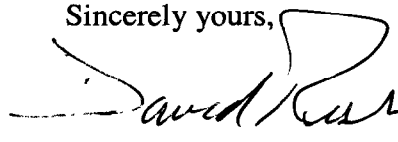
Line 782 onward - FDA should provide guidance for situations in which there is an imperfect (older) truth standard and the test agent is expected to perform better. How can superiority be shown when the "yardstick" is flawed? This is particularly important as many diagnostic procedures that FDA considers as truth standards are falling out of favor with clinicians and the unapproved tools are taking their place (e.g., DSA being replaced by CTA or MRA). Perhaps using multiple comparators as part of a panel of "truth" would help.

Lines 855 – 858 – we would like to request that the concept stated in these lines (i.e., compare the test agent both to the gold standard and a comparator) be revised to be more in line with the concept stated in Part II, Lines 301-303 ("...the only issue is comparing the accuracy of the new and old method"). Thus, a comparator should not necessarily be included in a study.

Line 903 onward – This section is lacking in any guidance on hypothesis generation, sample size, power, etc.

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

Sincerely yours,



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

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