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September 8, 2005

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

Re: Docket No. 2005D-0223  
Draft Guidance for Industry on Nonclinical Evaluation of Late Radiation Toxicity  
of Therapeutic Radiopharmaceuticals

Dear Sir or Madam:

Bracco Diagnostics Inc. is a global leader in the development and marketing of diagnostic imaging agents and radiopharmaceutical drug products used in both the diagnosis and treatment of various diseases. Bracco is actively involved in the development of new and novel therapeutic radiopharmaceuticals intended for use in the treatment of cancer. We appreciate the opportunity to comment on the draft guidance on the nonclinical evaluation of late radiation toxicity of therapeutic radiopharmaceuticals.

We commend the agency for their efforts in drafting this document and providing an important outline of the requirements for such nonclinical testing. In particular, we share the agency's concern that late-occurring radiation toxicities should be minimized whenever possible during the clinical trials of therapeutic radiopharmaceuticals. We believe that the draft guidance document represents an important step toward achieving this goal. We strongly recommend, however, that the agency balance this concern with the need to develop effective cancer therapies in a timely manner. Our comments, as presented below, are intended to provide clarification and aid in the development of a practical guidance document that will be of benefit to all involved in this important area of clinical research and drug development.

Our comments relate to the various sections of the draft guidance document as follows:

#### **I. INTRODUCTION**

The second paragraph indicates that this guidance is not intended for radiobiologicals (e.g., radiolabeled monoclonal antibodies). The reasoning provided for this exclusion is

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the lack of an established animal model for human biodistribution and the associated residence time of such agents. We question the categorical exclusion of radiobiologicals on this basis.

There are many cases in which appropriate animal models are not available for chemically derived radiotherapeutics as well. It cannot be assumed that because mouse, rat and dog models have been used traditionally to investigate the biodistribution of investigational products that these models are always suitable for such purposes. The guidance document must acknowledge that, in addition to radiobiologicals there may exist other situations in which the guidance is not appropriate; i.e., when a suitable animal model does not exist. This exclusion needs to apply to all investigational radiotherapeutics, whether biologically derived or not.

#### **IV. B. LATE RADIATION TOXICITY NONCLINICAL STUDY DESIGN**

##### **3. TIMING OF THE STUDY**

The draft document states that in order to select the most appropriate species, human dosimetry and pharmacokinetic data should be obtained before the nonclinical late radiation toxicity study is performed. It goes on to say that the nonclinical studies should ideally be completed before the start of Phase 2 dose escalation studies and that in certain cases a Phase 2 study can be initiated before complete submission of the data from the late radiation toxicity study based on a risk-benefit analysis. We have several concerns with the timing of the studies as described in the draft guidance document.

As the agency is well aware, drug development timelines are critical to both the patients for whom these agents are being developed and to the pharmaceutical companies conducting the research. As described in the General Test Design section of the guidance document these studies are expected to take 1 year post-dosing. Together with the time required for pre-study activities and post-study analyses, such a study will easily require 18 to 24 months to complete.

This requirement will impose a significant delay in the development of new cancer fighting drugs. As currently written the guideline will impose up to a 24 month hiatus in the clinical research program; i.e., the time between completion of the Phase 1 study which will provide the human dosimetry and PK data needed to select the appropriate animal species and completion of the nonclinical late radiation toxicity study which will be required prior to initiation of the Phase 2 study. This additional time requirement will have a significant negative impact on the ability to provide new treatment options to cancer patients as well as on the economics of drug development.

It must be recognized that in many cases therapeutic radiopharmaceuticals are being developed to treat patients with no other viable treatment options. In considering the risk-benefit options for these patients, they will not survive without the availability of new treatments. And in fact, even with these new agents they may not survive long enough to be impacted by late radiation toxicity.

Admittedly this is an extremely complex area that ultimately leads to striving to provide the best available options for patients and their families. We have serious concerns that this new guidance document will impose a significant delay in making new treatment options available. The statement that "In certain cases, a phase 2 clinical study can be initiated before complete submission of the data..." is not sufficiently clear nor does it obviate the delay that this guideline will impose. We recommend that the agency reconsider the timing for the nonclinical late radiation toxicity study and suggest that in most cases it be conducted in parallel with the Phase 2 program. Certain exceptions, based on unfavorable risk-benefit analyses, could be provided for in the document and in those specific cases the nonclinical study could be required prior to the Phase 2 trials.

#### **4. GENERAL STUDY DESIGN**

The draft guidance recommends that the nonclinical study design should closely mimic the anticipated design of the clinical studies, taking into account injected radioactivity, number of doses, frequency of dosing, etc. We agree with this concept, however, if the nonclinical study is performed as early as the draft document suggests there will not be sufficient information available regarding the anticipated clinical usage of the agent. This could even lead to having to repeat the nonclinical study once additional information is available. We again reiterate our point regarding timing of the nonclinical study. The guidance document should not require that the study be conducted prior to initiation Phase 2 trials.

In many cases information derived from patients during Phase 2 trials will be needed to properly design the nonclinical study. In some cases human data may be available following long-term follow-up in treated patients prior to design of the nonclinical study (e.g., when a drug is first developed outside the United States). These data should be considered when assessing the relevance of the nonclinical study and in some cases might be sufficient to obviate the need for such a study. The draft guidance document needs to take such data into account and provide clear alternatives when appropriate.

Thank you for the opportunity to comment on this draft guidance document. Should you have any questions regarding our comments please contact me at you convenience. We look forward to working with the agency to develop a practical working document to address this important area.

Sincerely,



J. Kris Piper  
Vice President  
Global Preclinical and Clinical Regulatory Affairs