SNM
Advancing Molecular Imaging and Therapy

October 18, 2011

Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
Food and Drug Administration
Division of Dockets Management [HFA-305]
5630 Fishers Lane, Rm. 1601
Rockville, MD 20852

VIA ELECTRONIC SUBMISSION

Re: Food and Drug Administration: Docket No. FDA-2011-D-0586; Draft Guidance for Industry on Standards for Clinical Trial Imaging Endpoints

Dear Dr. Woodcock:

We are writing to you in response to the Food and Drug Administration's (FDA) request for comments on draft guidance for industry on clinical trial imaging endpoints as published in the Federal Register (Vol. 76, No. 161) on August 19, 2011. The Society of Nuclear Medicine (SNM) is an international scientific and professional organization that promotes the science, technology and practical application of nuclear medicine. We represent 17,000 physicians, technologists and scientists specializing in research and the practice of nuclear medicine.

The Introduction of the guidance document states "This guidance focuses on the imaging standards that we regard as important when imaging is used to assess a primary endpoint, or an endpoint component, in a clinical trial intended to confirm aa drug's efficacy". Many FDG-PET trials are either in earlier Phase I or II trials and/or are used for secondary or exploratory endpoints. FDA should clarify whether imaging data would be considered valid if the trials did not conform to this standard but were used as secondary endpoints and/or in Phase I/II trials.

Furthermore, it is emphasized that clinical trial imaging standards should be used in confirmatory trials and are a higher standard than medical practice imaging standards. For many FDG-PET trials, the initial baseline scan may be performed as standard of care (e.g. staging) and reimbursed through third party insurance. SNM requests clarification on whether FDA intends to imply that the baseline scan must be repeated.

Relative to image interpretation being blinded to clinical data, in some cases, clinical information is needed to rule out metastatic disease. We would recommend that an exception be granted in certain cases. For the pre-study Imaging Charter development, we would request that the FDA refer to the UPICT document.

Regarding the instructions for vendor-specific equipment/platforms, FDA urges sponsors to use only FDA-approved or cleared analysis software. Because of the very limited role of the software in the clinic, this may not always be necessary or possible. Certain types of kinetic modeling software, for example, may never receive FDA approval, but could be essential for a clinical trial. SNM recommends FDA stipulate specifications that would qualify software for FDA approval thereby informing users of the essential elements that the equipment or software should meet.

There is a request for the sponsors to provide specific vendors, models, versions, and upgrades of all hardware/software that will be used in a trial. This information is typically not obtained until after the approval and initiation of the trial and in many cases does not include all of the information recommended. In theory, the SNM Clinical Trials Network (CTN) may be in a position to supply this informaiton to study sponsors prior to study initiation, but currently that is site-dependent. While this is information is important and could be collected throughout the study, we recommend that it not be required prior to study start.

Additionally, FDA recommends providing specific technical acquisition settings for each device that is used in a trial. Currently most trials use more generic guidelines because this knowledge is currently not available. The CTN Image Reconstruction and Harmonization Group is conducting research to develop this data, however, the results are several years away. We would recommend that this not be required at this time.

SNM is encouraged by the inclusion of guidance for using phantoms for site qualification and image quality monitoring. A phantom mimics lesions in the human torso and provides quantitative, and sometimes qualitative, information in conditions similar to actual clinical imaging settings. Use of phantoms across study centers helps to ensure PET/CT scanner images are comparable and reproducible across multiple study sites for image noise and texture, quantitative accuracy and lesion detectability, thereby promoting standardization. The CTN has accumulated scanner data on over 140 scanners using the unique anthropomorphic clinical simulator chest phantom.

SNM supports the direction regarding site qualification process and quality control monitoring. Site qualification will help to ensure a level of standardization across all study sites. On-site monitoring in the PET/CT department will allow for better protocol adherence and understanding. However, in practice, most trial monitors do not have sufficient knowledge or training to do this and there are major resource challenges for organizations such as CTN or even CROs to do this onsite.

The SNM recommends FDA change the heading at line 506, and the content of the paragraph which follows, to ***radiopharmaceutical*** instead of radionuclide agents. Additionally, the SNM recommends FDA change the statement at line 508, “In addition to specification of the dose and route of administration…” to read “In addition to specification of the ***administered activity*** and route of administration…”as the term ‘dose’ can be ambiguous for decaying, radiopharmaceutical products.

In Section C: Clinical Trial Standards for Image Interpretation, quantification is mentioned as an adjunct to visual interpretation. With the advancements in the PET cameras, reconstruction parameters, and radiopharmaceuticals, accurate measurement of quantitative values, such as SUV, are critical and often an endpoint criteria. SNM therefore recommends FDA better reflect this essential element in the text.

The SNM applauds the efforts of the FDA to standardize imaging procedures when an imaging endpoint is used in a clinical trial of a therapeutic or biologic drug product. This guidance will prove valuable for the sponsors of trials and provide areas for discussion with imaging professionals. If you have any questions, please contact Sue Bunning, Director of Health Policy and Regulatory Affairs, sbunning@snm.org or (703) 326-1182.

Sincerely,

George Segall, MD
President

CC: Fred Fahey, DSc
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