MEETING SUMMARY

MEETING SUBJECT:	**Pharma Imaging Group 2012 Telecon**
DATE / TIME:	**30 Mar 2012 / 11:00am EST**
ATTENDEES:	Raphael Dwaine Rieves, MD; Alex Gorovets, MD; L. Marzella, MD, PhD
PREPARED BY: (printed & signature)	**Allison Andrews, G Goldmacher, J Conklin, D Mozley**
LOCATION	**Teleconference**

SUMMARY: Discussion of 2011 FDA Guidance for Industry:

Standards for Clinical Trial Imaging Endpoints

DISCUSSION POINTS:

1. 2011 FDA Guidance on Imaging Endpoints

Discussion led by Raphael Dwaine Rieves, MD

- Introduce staff also on line
  - Dr. Louis Marzella
  - Dr. Alex Gorovets
- Guidance Development Process
  - In final stages, but not final steps
  - Draft was sent out for public review
  - Received about 20 documents of comments from a variety of groups and individuals
  - Reviewed all comments and made efforts to address themes and some isolated issues
  - Planning to finalize draft
    - Still internal document
  - Next will go to Office of New Drugs
    - Includes therapeutic review divisions
  - Will continue to receive questions and feedback that will need to be modified in the document

- Broader FDA audience input
- Clearance process, final editing (format)
- Posted on website as final guidance
- Final guidance could be revised after a period of time

- 15 points from feedback
  - May overlook some points, welcome questions and feedback
  - In the opening text, make it clear that this guidance pertains to imaging only in confirmatory clinical trials of therapeutic drugs
    - Focuses on standards that FDA regards as important with imaging issues to assess the trials primary endpoint
    - Will mention imaging may have a role in other components in a study (ex. Safety monitoring)
  - This guidance does not address if imaging outcome is clinically meaningful
    - Does not address if an imaging outcome is acceptable for drug approval evidence
    - This determination requires far more than consideration of imaging standardization
    - Guidance documents come out for specific areas
    - Guidance solely deals with standardization of imaging
  - Guidance does not address Biomarker Qualification Review Team process (own draft guidance)
  - Guidance follows same architecture that the draft did
    - Start out with medical practice standard vs. clinical trial standard
  - Series of questions and answers at the beginning of the document
    - Anticipate the audience to be very broad
    - Some may have peripheral interest in imaging, more interest in clinical trial development without imaging focus
    - Directed at clinical trialists rather than imaging professionals
  - Explain potential for imbalance in study arms related to image acquisition times
    - Imaging evaluations are scheduled not based on calendar days, but are tied to cycles
    - ***Include comment to encourage trialists to schedule evaluations based on calendar days, not cycles***
  - Imaging Charter can be single document or ensemble document

- Can include acquisition manuals, reader manuals, and other technical manuals
- Charter may, or may not be, a component of the protocol if sponsors prefer this
- FDA does not generally regard the Imaging Charter as a component of the trial's clinical protocol
- FDA does not require submission of Charter coincident with the submission of clinical protocol for FDA review
- FDA encourages submission of charters as soon as possible and encourages submission of charters with special protocol assessments that are submitted to the agency (but even in this circumstance, it is not required)
- Imaging Charter is not typically regarded as part of the agreement that follows FDA concurrence upon a clinical trial protocol

o Encourage discussion of the role of the Imaging Charter at end of Phase II meetings, especially as they may apply to a special protocol assessment
  - Leads to the possibility for therapeutic review division to provide comment

o Guidance states that FDA does not require a format for Imaging Charter or content of the Imaging Charter
  - Address or consider aspects when developing charter to try to optimize standardization of imaging

o Describes specific aspects of imaging standardization
  - Modify some of the subtext

o Charter should identify use of any investigational equipment
  - For international trials, encourages use of equipment that is lawfully marketed in the area

o Potential usefulness of Phantoms in assisting with acquisition standardization
  - Does not require use of phantoms
  - Phantoms may or may not be necessary depending on the nature of imaging in the trial

o Brief subsection on imaging risk
  - Guidance notes that imaging risks are best described in the clinical protocol and addressed in consent documents
  - Anticipate charters will not typically contain a section that describes imaging risks, but should be described in clinical protocol and consent document

	o Incidental Findings ▪ Common theme among the comments, modified section ▪ Emphasizes need for clinical protocol to describe how incidental findings will be handled, and only if applicable, describe how these will be handled in the charter ▪ "In general, we anticipate that incidental imaging findings likely to have important clinical consequences such as life threatening conditions, serious conditions that can be treated or prevented will, as should be described in the study protocol, be disclosed to the site investigator, who in turn evaluates the value and role of the observation in patient management." o Amount of site monitoring of image acquisition qualities o New Section – Brief section that describes the importance of the professional staff ensuring the fidelity of the charter or the components of the charter with the clinical protocol ▪ "We encourage imaging charters to include a brief section that clearly states all imaging technical documents will be reviewed to ensure that the imaging specific details produce outcomes consistent with the trial's clinical protocol." ▪ Some trials have contractors and subcontractors developing documents that define the imaging, and there have been cases where the downstream documents are inconsistent with the goals of the protocol (ex. eCRF collects information not consistent with the primary endpoint) ▪ Encourage sponsors to have an individual or small group of individuals knowledgeable in both clinical trials and imaging who are responsible for integrating the imaging-related documents for the trial, to make sure that the technical details are consistent with the trial as a whole
2.	**Questions and Answers** • Dr. Colin Miller – Incidental findings - "Has any consideration been given to requiring or making a statement in the guidance document to the fact of needing something for consent regarding incidental findings?" Reference thesis Wolf et. al – proposed that if ICF specifies no duty to report, that relieves the duty ethically. o DR: Tried to specifically cite that, you need to have incidental findings addressed in the clinical protocol as well as to emphasize in the informed consent. Guidance does not state specifically how to handle them. Do not go into great detail, but will look at it again in protocol and consent document. • Dr. Jim Conklin – In 2007, PHARMA/DIA/FDA had meetings where a draft charter Table of Contents was determined. "Did the agency find that those

charters in that format were easier to review?"

- DR: At one stage of the evolution, excerpted as appendix in working document. Some found that it was redundant. Regard TOC as very useful. The document was marked "Confidential and Proprietary", did not feel comfortable excerpting that text. Did not plagiarize.
- ***David Mozley: Intent was to have everyone cut and paste the table of contents. Did not get it published as planned.***

- Dr. Rick Jacobs – Follow up on Colin's question – Scenario: If an oncology trial is collecting images, but these images are not reviewed until a year later, and on review, the radiologist sees something else. "Would it be appropriate in the charter to describe the timing of the review and the need or lack of need for reporting something like that so far removed from the clinical time frame?"
  - DR: Guidance will encourage trialists to address this up front. Ideally the protocol and consent document talk about those situations. The lead medical officer for each clinical trial will bear the ultimate responsibility as they do with other findings (laboratory tests). Medical monitor or Chief Medical Officer for trial to handle it. It gets back to anticipating and getting the processes for handling it into the protocol and the consent.
  - RJ: Specific question related to timing. Does the timing affect the intent?
  - DM: Did you shift your prose so that the emphasis on detecting and acting on incidental findings falls within the requirements of the protocol and no longer resides as an integral part of the imaging charter as it seemed to be during the first draft?
  - DR: Yes. It's shifted out of the imaging charter and into the protocol and consent document.
- Mary Ann Battles – Table of Contents – Discussion in organization around need to include potential readers who are analyzing the primary endpoint data for a study to get financial disclosures from them and include on 1572.
  - DR: Did not address this in the guidance. Regard the readers as sub-sub-investigators. We usually get financial disclosures. This is a good topic, and we'll bring it up with our working group. We could include a statement about how the trial views image readers.
  - DM: In an ideal world, image analysts are completely blind to the clinical circumstances surrounding the trial. What negative impact could that payment have in the real world?
  - MAB: Some of the discussion we've had is they would not be listed on the 1572 because the site investigator has no control over the oversight and training of these individuals. Strong feelings that potentially the imaging supplier should ensure that there is no financial or scientific conflict of interest in the imaging readers who are assigned to read images for a particular sponsor. Also ensure that as part of the charter and contract with the vendor.
  - DR: Share among working group, might be useful for some elaboration.

	Do not include a subsection on this, but will do our best to address this.
3.	**Announcements** • June timeframe after ASCO, Dr. Larry Schwartz (Chairman of Radiology at Columbia University Hospital) will provide update on RECIST discussions • Send topics to Dr. Conklin and Dr. Mozley that you would like to discuss through the end of September