Medical Imaging:
CDER’s Perspective

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2 Topics: 2 Days

• Standardization of imaging in clinical trials

and

• Current Good Manufacturing Practices (CGMPs) for PET drugs…

FR publication 12/2009
Not Disparate Topics…

Day one:
• **Standardization** of image acquisition, interpretation, and management of data in multicenter clinical trials is essential for accurate **diagnosis and to assess response to therapies**

Day 2:
• **Standardization of PET Radiopharmaceuticals** production under CGMP 21 CFR 212

This workshop will help us all achieve our goals of facilitating the public access to important, safe and effective products
Imaging in Clinical Trials

• Long history of use in exploratory and confirmatory clinical trials, e.g.,
  – coronary arteriographic patency important to the development of thrombolytic agents in the 1980’s and early 90’s
  – Changes in tumor size widely used to detect oncologic drug efficacy

• Imaging: essential for accurate diagnosis and in most therapeutic area clinical trials
Importance of Standardization in Trials

- Rapid advances in imaging technology-- increased potential for site-to-site variability in imaging data

- Variability may obscure treatment effects and complicate data verification

- Multiple challenges given wide role for imaging
  - Selection of patients (eligibility)
  - Safety (e.g., decreased ejection fraction)
  - Efficacy (e.g., change in joint architecture or tumor size)
Importance of Standardization in Trials

- Emphasized in the 2007 PDUFA agreements where FDA agreed to develop (by end of 2011) a guidance document on “Imaging Standards for Endpoints in Clinical Trials”

- In this workshop, FDA wants to hear your thoughts on standardization

- Your feedback will inform the imaging guidance:
  - What do you regard as important?
  - How is this standardization best accomplished?
PET CGMP (day 2)

- Publication of PET CGMP (12/2009) has implications for the use of PET drugs in trials as well as clinical practice
- Law requires NDA or ANDA submission for any PET drug used in clinical practice (i.e., non-investigational use) within 2 yrs of CGMP publication (12/2011)
- Investigational PET drug use continues under IND or RDRC pathways
- FDA working to facilitate the submission of NDA and ANDAs for most commonly used PET drugs, e.g., F18-FDG
PET CGMP

• PET producers may find NDA/ANDA submission challenging, particularly the development of the PET drug production and testing information

• CGMP standards for PET drug production: focus of tomorrow’s sessions

• PET drug production “on site” necessitates consistency in the manufacturing process—an “added” standardization consideration for imaging in clinical trials
Imaging as a Biomarker

• Concept: Biomarker qualification is a conclusion that within the stated context of use, the results of biomarker measurements (e.g. imaging) or can be relied upon to have a stated interpretation and utility.

• Context of use must be clearly specified.

• Regulatory implication: Industry relies upon use of the biomarker in the qualified manner in IND, NDA and BLA submissions, without a need to resubmit data for the relevant CDER review group to consider and reconfirm the biomarker usage.
Qualified Biomarker Usage

• The use of a qualified imaging biomarker can be applied in drug development and evaluation if there are NO:

  – Serious study flaws (e.g., unverifiable data, improper performance of assays, etc.)
  – Intention to apply the imaging biomarker outside the qualified context of use
  – New and conflicting scientific facts not known at the time the qualification was determined
Qualification Process in General

• A framework for interactions between CDER and sponsors so that CDER can provide guidance towards compiling comprehensive evidence to support qualification of the selected biomarker(s), including imaging biomarkers

• A mechanism enabling CDER to have a well-organized, multi-discipline, CDER-unified, formal review of the data supporting a biomarker, eventually leading to a CDER decision on qualification

• Enables a scientifically well-supported statement by CDER of qualification providing confidence that the evaluation has been comprehensive and the conclusions can be relied upon
Qualification Process within CDER

• Formalized process still under development

• ‘Sponsor’ brings imaging biomarker concept/information package to CDER

• Interdisciplinary working team assembled within CDER & other FDA components

• Information Package reviewed

• Advice given on how to further progress development for intended use
  – Consultation and advice
  – Continued until development is complete

• Full detailed CDER review and decision on qualification

• Formal statement of qualification if appropriate
Points of Contact at CDER

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Summary

• Standardization of production and use of imaging technologies will facilitate use in drug (and device) development trials, and uptake in clinical practice

• FDA intends to work with the community in standards development
Summary

• The biomarker qualification process will be useful when considering use of an imaging technology as an important component in a drug development process
• Initiating qualification of an imaging biomarker will be contingent upon adequate standardization of the particular imaging process