

**Peripheral and Central Nervous
System Drugs Advisory Committee
Meeting**

**Clinical Development of
Radionuclide Imaging Products for
the Detection of Amyloid to Assist
in the Diagnosis of Alzheimer's
Disease**

October 23, 2008

Dwaine Rieves, M.D.

Diagnostic Effectiveness: Confirmatory Clinical Study Considerations

■ Performance characteristics

- sensitivity, specificity**

■ Clinically useful information

- “well-established” or self-evident**
- established in clinical studies**

■ To what extent would a test that detects brain amyloid provide clinically useful information?

- if usefulness is “self-evident,” define PC
- if not, establish usefulness in studies

■ What are acceptable comparators for performance characteristics determination?

Background

- Requests for assistance in designing phase 3 studies
- Requested outlines
- 3 Companies responded
- “amyloid detection” vs “diagnosis of Alzheimer’s Disease”

Background

- **We are not focusing upon:**
 - any specific product
 - any recommendations for specific regulatory action
- **We are focusing upon shared:**
 - perspectives and data from companies
 - regulatory expectations
 - perspectives from AC members

Agenda

- **FDA: Overview of imaging claims**
- **Dr. Madhav Thambisetty:**
Clinical Presentation, Diagnosis and Management of Alzheimer's Disease
- **Dr. William Rebeck:**
Amyloid and Amyloid Deposition in the Brain
- **Break**
- **Companies: Avid Radiopharmaceuticals, Bayer Health Care Pharmaceuticals, GE Healthcare**
- **FDA introduction to questions**
- **Lunch and Afternoon Discussions**

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Overview of Potential Imaging Claims

Alexander Gorovets, MD
Medical Officer Team Leader
Division of Medical Imaging and
Hematology Products

Diagnostic Imaging Agents:

- Regulations
- Guidances
- Amyloid Imaging

Diagnostic Radiopharmaceuticals

- **A radionuclide that can be detected *in vivo***
 - Technetium-99m,
 - Iodine-123
 - Fluorine-18
- **A nonradioactive component that delivers the radionuclide to specific areas within the body**
 - antibody
 - ligand for receptor

Code of Federal Regulations

Part 315

“The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use”

- Proposed indications
- Useful clinical information

315.4 Indications

- 1 - Structure delineation
- 2 - Functional, physiological, or biochemical assessment;
- 3 - Disease or pathology detection or assessment; and
- 4 - Diagnostic or therapeutic patient management.

315.5 Effectiveness: Useful Clinical Information

“determined by a comparison with a reliable assessment of actual clinical status”

- ***Effectiveness: comparison to a standard***
- ***Diagnostic information must be clinically useful***

Guidance for Industry - 2004

Developing Medical Imaging Drug and Biological Products

Part 1: Safety

Part 2: Clinical Indications

**Part 3: Design, Analysis, and
Interpretation of Clinical Studies**

Guidance: Indications

■ Structure delineation

- *normal versus abnormal bronchi, knee cartilage*

■ Disease or pathology detection or assessment

- *location of a mass with specific tumor antigens*

■ Functional, physiological, or biochemical assessment

- *ejection fraction*

■ Diagnostic or therapeutic patient management

- *coronary artery disease*

Guidance: Effectiveness

1- Test accuracy

2- Clinical value

Guidance: Test Accuracy

- **Determined by a comparison to a truth standard (e.g., histopathology) or a reference test of known reliability (e.g., previously approved test)**
 - **Sensitivity**
 - **Specificity**
- **In absence of truth standard or reference test, establish the clinical usefulness of the information**

Guidance: Clinical Value

- **May already known to be clinically useful, e.g., for structure delineation or pathology detection**
- **Where clinical value is not established, data should establish the value of the diagnostic information**
- **“Simply generating an image, for which the implications to the patient are not understood, does not confer benefits to the patient.”**

“Detection of Amyloid” vs. “Alzheimer’s Disease Diagnosis”

- **Amyloid detection:**
 - a “pathology” indication
- **Alzheimer’s Disease:**
 - a specific diagnosis

Effectiveness: “Amyloid Detection”

- **Is it clinically useful?**

- If not, studies should establish the clinical usefulness of the diagnostic information

- **What is the appropriate truth standard or reference test?**

- If no appropriate truth standard or reference test, studies should establish the clinical usefulness of the diagnostic information

Summary

- **Variety of potential indications**
- **Effectiveness assessment generally based upon performance characteristics as related to SOT**
- **Value of diagnostic information**
 - known to be clinically useful, or
 - established in clinical studies

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FDA Introduction to Questions

Qi Feng, M.D., Ph.D.

Medical Officer

Division of Medical Imaging and Hematology Products

OODP, OND, CDER, FDA

Indications for Medical Imaging Agents

- **Structure delineation**
- **Disease or **pathology detection** or assessment**
- **Functional, physiological, or biochemical assessment**
- **Clinical diagnosis or therapeutic patient management assessment**

- **Draft Indication Statements**
- **Draft Protocol Outlines**
 - **Patients**
 - **Standard of truth (SOT)**
 - **Primary endpoint**

Avid

“indicated for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment”

Avid: Draft Protocol Outline

Patients: life expectancy \leq 6 months, 1/3 with AD or mild cognitive impairment (MCI), participate in brain donation

SOT: autopsy brain amyloid

Primary endpoint: correspondence between scan of low cortical amyloid and autopsy evaluation of plaque burden among patients who die within 12 months of scan

Bayer

“(Product) can detect amyloid beta plaque deposition in the brain and thereby, assist the physician in the diagnosis of (detection/exclusion) of Alzheimer’s disease.”

Bayer: Draft Protocol Outline

Patients: healthy volunteers and patients with cognitive impairment

SOT: Expert panel diagnosis of prob AD

Primary endpoint: sensitivity & specificity in subset of patients who are either healthy or diagnosed with prob AD

GE

“Detection of β amyloid deposits in the brain.”

GE: Draft Protocol Outline

Patients: healthy volunteers and patients with MCI or AD

SOT: C-11 PIB

Primary endpoint: comparability of imaging findings between C-11 PIB and studying agent

Amyloid Detection: Clinical Value

- **Self-evident**

or

- **Established in clinical studies**

Question # 1:

To what extent, if any, would an indication for use of an *in vivo* diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?

Question # 2:

If an *in vivo* diagnostic radiopharmaceutical is clinically useful in the "detection of cerebral amyloid," what should be a "standard of truth" in phase 3 clinical studies?

Request # 3:

Please comment on the strengths and weaknesses of the **phase-3 study outlines supplied by the companies.**

Please consider:

- Patients**
- SOT**
- Primary endpoints**

THANK YOU