2012 FDA Update

"High Country Meeting"

March 5, 2012/11:30 EST

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Focus on Imaging Drugs…

- **Drug approvals & labeling actions**
- **Standardization guidance**
- **Medical Imaging Drug Advisory Committee (MIDAC)**
- **Positron Emission Tomography (PET) topics**

2011/12 Imaging Drug Approvals & Labeling Actions

Gadobutrol Injection (Gadavist)	NDA (Bayer)
Fludeoxyglucose F18 Injection	ANDA (PETNET)
Perflutren lipid microsphere injectable suspension (Definity®)	NDA supplement (Lantheus)
Rubidium Rb 82 chloride injection (CardioGen-82®)	NDA supplement (Bracco)

Draft "Standardization" Guidance

Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Final guidance targeted for October, 2012

Medical Imaging Drugs Advisory Committee (MIDAC)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2011–N–0002]

Advisory Committee; Medical Imaging Drugs Advisory Committee; Reestablishment

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the

Nominees undergoing vetting process

Positron Emission Tomography (PET) Drugs

"PET Drug Website"

Goto:

http://www.fda.gov/

In search box, place:

"PET Drug Manufacturing"

Updates, Guidances, Presentations, Historical Information…*and more*…

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Development & Approval Process (Drugs)

- Manufacturing
- Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations
- Positron Emission Tomography (PET)
- Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs
- Current Good Manufacturing Practices for Drugs: Reports, Guidances and Additional Information

Resources for You

Positron Emission Tomography (PET)

Notice of FDA Exercise of Enforcement Discretion for PET Drugs

In 1997, Congress passed the Food and Drug Administration Modernization Act (Public Law 105-115) (the Modernization Act). Section 121 of the Modernization Act directed FDA to establish appropriate approval procedures and Current Good Manufacturing Practices (CGMP) for PET drugs. These procedures were published on December 9, 2009, triggering an implementation timeline. Under the requirements of section 121, within 2 years of that publication date, a new drug application (NDA) or abbreviated new drug application (ANDA) must be submitted for any PET drug marketed for clinical use in the United States.

Recently, FDA has received requests to extend the application submission deadline from and on behalf of some PET drug producers trying to comply with the regulation and application submission requirements. Some firms have expressed concern that if they are unable to submit their application by December 12, 2011, they will have to halt production of PET drugs for use in clinical care of patients. Further, although we do not anticipate any shortages of PET drugs after December 12, 2011, we are concerned that sole producers in isolated areas may halt production if their application has not been submitted and this could create a barrier to access in that particular area. Having considered these points, in addition to the fact that we have yet to issue the two instructive guidances for PET drug producers *(Investigational New Drug Applications for PET Drugs and FDA Regulation of PET Drug Products, Questions and Answers)* that are currently under development, FDA has decided to exercise enforcement discretion under the following circumstances until June 12, 2012.

For the next six months, until June 12, 2012, FDA does not intend to take enforcement action against a PET facility currently producing PET drugs for clinical use for a failure to submit a new drug application by December 12, 2011, provided that the facility complies with all other FDA requirements, including current good manufacturing practices (CGMPs). **FDA will not exercise enforcement discretion after June 12, 2012.**

PET Drug
Current Good Manufacturing Practices (cGMP)
Background

1997	**FDA Modernization Act** • Required cGMP for PET • 2 yrs post-publication NDA/ANDA for any PET drug in "clinical use"
2009 Dec	**FDA publishes PET Drugs cGMP** • NDA/ANDA due by 12/12/2011
2011 Dec	**Notice of enforcement discretion** • NDA/ANDA due by 06/12/2012 for any PET drug in "clinical use"

PET Presentations / Seminars

Pre-2009	Multiple presentations/draft info
2009 - 2011	FDA seminars at SNM Annual Meetings; Planned for 2012
2010 Apr	FDA PET Drug Workshop
2011 Mar	FDA PET Drug Public Meeting
2012 Jan	FDA webinar on cGMP… *Still available on the FDA "PET Drug website"*

PET Drug Guidances

2011	**PET Drug Applications:** **Content & Format for** **FDG F18 / Ammonia N13 / Fluoride F18**
2011	**Media Fills for Validation of Aseptic Preparations (draft)**
2012	**Questions and Answers…*new!***
2012	**Investigational New Drug (IND) Applications (draft)…*new!***

PET Drug Main Points

- **By June 12, 2012 must have submitted NDA/ANDA for any drug in "clinical use" *or* the "clinical use" must be under an IND**

- **By December 12, 2015 must have an approved NDA/ANDA or an effective IND for the "clinical use"**

"Use" Phrases

"CLINICAL use" – PET drug is a component of clinical care/not a systematic study of drug safety-efficacy

- under NDA/ANDA *or* IND

"INVESTIGATIONAL use"– PET drug is studied to determine its safety-efficacy

- under IND *or* exempted from IND

"RESEARCH use" – PET drug is a component of a research project under Radioactive Drug Research Committee (RDRC) approval

- RDRC approval (no exemption option)

"*Expanded Access IND Submission*"

Intended to provide clinical access to investigational drugs for diagnostic / therapeutic monitoring purposes

- **Can be an original IND submission or a submission to an existing IND**
- **Applies to limited situations defined by criteria**
- **May be submitted with a "Request to Charge"**

Expanded Access Criteria

1) **Patient(s) with serious or immediately life-threatening disease / condition**

2) **No comparable/satisfactory alternative "therapy"**

3) **Potential benefit justifies the potential risk of the clinical use**

4) **Provision of drug will not interfere with drug development for market approval**

Expanded Access (EA) Criteria Interpretation (p1 of 2)

1) **Regarding serious or immediately life-threatening disease or condition,**

   FDA allows for use of PET drug to help detect a serious / life-threatening disease even if the condition not actively manifest

2) **No comparable/satisfactory alternative therapy**

   Necessitates justification of why alternative drugs are not satisfactory (e.g., PET drug's unique metabolic assessment activity)

Expanded Access (EA) Criteria Interpretation (p2 of 2)

3) **Potential benefit justifies the potential risk of the clinical use**

   Based on available evidence/prior experience/dosage/consideration of population characteristics (e.g., pediatrics)

4) **Provision of the drug will not interfere with drug development for market approval**

   FDA anticipates EA will only apply in situation where NDA/ANDA not feasible

Expanded Access Pointers

- **Expanded Access Submission Process**
  - ❖ **explained in IND guidance**
- **Not appropriate when an NDA/ANDA is feasible**
  - ❖ **not appropriate for FDG F18, ammonia N 13, sodium fluoride F18**
- **Clinical use may continue during the 30 day review period based upon prior clinical use / otherwise, the sponsor will be contacted**
- **If plan to charge, need to submit a "Request to Charge" submission to the IND**

"Request to Charge"

- **A submission process unique to an IND**
  - ❖ **described in PET IND guidance**
- **Charging may be requested for either**
  - ❖ **a clinical trial / investigation or**
  - ❖ **Expanded Access**
- **Certain criteria must be met before FDA authorizes charging**

"Request to Charge" Review Criteria -- Clinical Trial --

- **Potential benefit of investigational drug provides significant advantage over available products**
- **Clinical trial data essential for marketing support**
- **Cost of drug extraordinary**
- **Describe proposed cost (only direct costs)**
- **Statement that CPA has reviewed/approved cost calculations**

"Request to Charge" Review Criteria -- Expanded Access Program --

- **Assurance that charging will not interfere with developing the drug for marketing**
- **Describe proposed cost to be charged a patient (direct costs for single patient; direct + indirect costs for other)**
- **Statement that CPA has reviewed/approved cost calculations**

Other Special PET Drug IND Considerations

- **Prior to December 12, 2015, an IND may not be necessary *if* the PET drug is the subject of a submitted NDA/ANDA**

- **After December 12, 2015, all investigational use of a PET drug must be under an IND unless the use is exempted from IND**

- **Many studies using FDG F18 are currently ongoing outside of IND**
  - ❖ **these uses may continue until 12/12/2015 *if* the FDG F18 is the subject of a submitted NDA/ANDA**

Thank you!

Q & A

PET Drug Web address:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm

or

Go to http://www.fda.gov/ and search for "PET Drug Manufacturing"