

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202008Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202008

SUPPL #

HFD # 160

Trade Name Amyvid

Generic Name Florbetepir F18 (18F-AV-45)

Applicant Name Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Co.

Approval Date, If Known April 7, 2012

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

DRAFT

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1  
!  
! YES  NO   
! Explain: ! Explain:

Investigation #2  
!  
! YES  NO   
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Sharon Thomas  
Title: Regulatory Project Manager  
Date: March 23, 2012

Name of Office/Division Director signing form: Charles J. Ganley, M.D.  
Title: Director, Office of Drug Evaluation IV

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

### 1.3. Administrative Information

## **EXCLUSIVITY REQUEST**

Avid Radiopharmaceuticals, Inc. (Avid) hereby claims five years of marketing exclusivity, under 21 CFR 314.108(b)(2), from the date of approval of NDA 202,008 for florbetapir F 18 injection. To the best of Avid's knowledge or belief, a drug that contains florbetapir F 18 as the active moiety has not been previously approved under section 505(b) of the act.

This request for exclusivity is based upon the following:

A search of the FDA drug approvals database<sup>1</sup> conducted on 22 March 2012 for the term "florbetapir" did not return any results.

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<sup>1</sup> Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

DEBARMENT CERTIFICATION STATEMENT

Avid Radiopharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the service of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

  
\_\_\_\_\_  
Alan Carpenter, Ph.D., J.D.  
Vice President Legal and Regulatory Affairs

14-JULY-2010  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 202008 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Amyvid Established/Proper Name: Florbetapir (F 18) Dosage Form: Injection		Applicant: Avid Radiopharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Sharon Thomas		Division: Division of Medical Imaging Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2) Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>April 7, 2012</u></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input type="checkbox"/> None Complete Response, March 17, 2011	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required         </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) April 6, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	March 29, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	October 7, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	March 21, 2012
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	December 10, 2010 February 24, 2012 December 9, 2010
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM October 19, 2011 <input checked="" type="checkbox"/> DMEPA February 24, 2012 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) February 27, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews Maternal Health: January 18, 2012 and February 28, 2012 Peds: December 20, 2011
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>November 3, 2010</u> If PeRC review not necessary, explain: <u>Full Waiver Granted: November 16, 2010 PeRC review not necessary for 2<sup>nd</sup> Cycle.</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)</li> </ul>	March 18, 2011 May 3, 2011 May 11, 2011 May 13, 2011 May 19, 2011 June 10, 2011 June 14, 2011 August 23, 2011 August 29, 2011 September 1, 2011 September 16, 2011 October 6, 2011 October 7, 2011 November 4, 2011 November 7, 2011 November 30, 2012 February 21, 2012 (2) March 9, 2012 (2) March 16, 2012
<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	March 22, 2011 March 31, 2011 May 11, 2011 June 10, 2011 August 29, 2011 October 6, 2011 November 7, 2011 November 16, 2011 December 13, 2011
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg    Wrap-Up: March 6, 2012
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    July 15, 2010
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    May 18, 2009
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	January 20, 2011
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	February 9, 2011

<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 5, 2012
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 28, 2012
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 24, 2012
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None March 28, 2012
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	March 24, 2012
• Clinical review(s) ( <i>indicate date for each review</i> )	March 7, 2012
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See page 14- March 7, 2012 (Clinical Review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None January 5, 2011 (DNP)-1 <sup>st</sup> Cycle
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested January 19, 2012
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Concurred with Reviewer- March 14, 2012
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Concurred with Reviewer- March 14, 2012
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 14, 2012

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None Concurred with Reviewer- March 13, 2012
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None Concurred with Reviewer- March 13, 2012
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 13, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 27, 2012
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 21, 2012
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 17, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concurred with Reviewer- March 10, 2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None March 10, 2012
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed March 8, 2012
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC Review dated March 10, 2012
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	See CMC Review dated March 10, 2012

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within <b>2 years</b> of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites <sup>7</sup> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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SHARON P THOMAS  
04/06/2012

**From:** Thomas, Sharon  
**Sent:** Thursday, March 29, 2012 9:13 AM  
**To:** 'Stephen Truocchio'  
**Subject:** Labeling- NDA 202008- Amyvid

**Attachments:** FDA\_to\_Avid\_bulk\_shield\_2012\_0329).doc; FDA\_to\_Avid\_2012\_0329.docx

## **LABELING DISCUSSION COMMENTS**

Avid Radiopharmaceuticals, Inc.  
Attention: Stephen P. Truocchio, M.S., RAC  
Senior Director, Regulatory Affairs

Dear Mr. Truocchio:

Please refer to your October 7, 2011 New Drug Application (NDA) resubmission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir F 18) Injection.

Attached are our draft redline versions of the PI and container labels which will serve as a basis for our discussion in today's teleconference. Please don't hesitate to contact me if you have any questions.

Thank you,

Sharon

\*\*\*\*\*

Sharon P. Thomas  
Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV - CDER - FDA

Phone: 301-796-1994  
Fax: 301: 796-9849  
sharon.thomas@fda.hhs.gov



FDA\_to\_Avid\_bulk\_  
shield\_2012\_0...



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/s/  
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SHARON P THOMAS  
03/29/2012

**Subject:** FW: PMCs- NDA 202008- Amyvid

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**From:** Thomas, Sharon  
**Sent:** Thursday, March 29, 2012 11:05 AM  
**To:** 'Stephen Trucchio'  
**Subject:** PMCs- NDA 202008- Amyvid

## **POST-MARKETING COMMITMENTS (PMCs)**

Avid Radiopharmaceuticals, Inc.  
Attention: Stephen P. Trucchio, M.S., RAC  
Senior Director, Regulatory Affairs

Dear Mr. Trucchio:

Please refer to your October 7, 2011 New Drug Application (NDA) resubmission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir F 18) Injection.

We are requesting your concurrence to conduct two post-marketing commitment clinical studies as outlined below. The main focus of these studies is agreed upon between the FDA and the NDA applicant prior to approval of the application. We offer the following proposal (text to be included in an action letter with time lines). We encourage you to examine these proposals and make necessary revisions, then return the proposals to us (with time lines) as soon as possible. The dates cited below are solely as examples; modify to fit the format.

### **POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B.**

1. To conduct a clinical study that will compare the results of Amyvid scan interpretations at local clinical sites to interpretations performed by an expert(s) at a central reading facility. The main objectives of this study are to assess the reliability of Amyvid scan interpretations as they are performed in clinical practice and to help determine the sufficiency of the reader training process. The study will include readers trained using an in-person training program as well as readers trained using the electronic self-study method.

The timetable you submitted on March XX, 2012 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	December XX, 2012
Final Protocol Submission:	June XX, 2013
Final Report Submission:	June XX, 2014

2. To conduct a clinical study that will explore the use of standard uptake value ratio (SUVR) and/or other quantitative outcomes at local clinical sites as an adjunct to

qualitative Amyvid scan interpretations. The main objective of this study is to assess the feasibility of implementing a quantitative process for Amyvid scan interpretation by clinical sites that will enhance the reliability of scan interpretations in clinical practice. The study will pre-specify a threshold SUVR for binary determination of amyloid neuritic plaque density (positive or negative).

The timetable you submitted on March XX, 2012 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	December XX, 2012
Final Protocol Submission:	June XX, 2013
Final Report Submission:	June XX, 2014

We will discuss the PMCs in greater detail today's tcon. Should you have any questions, please don't hesitate to contact me.

Thank You,

*Sharon*

Sharon Thomas, RPM  
Division of Medical Imaging Products  
Office of Drug Evaluation IV, CDER, FDA  
Phone: (301) 796-1994  
Fax: (301) 796-9849  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

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/s/  
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SHARON P THOMAS  
03/29/2012

**From:** Davis-Warren, Alberta E  
**Sent:** Friday, March 16, 2012 1:42 PM  
**To:** 'truocchio@avidrp.com'  
**Cc:** 'whitelevine@avidrp.com'; Thomas, Sharon  
**Subject:** NDA 202008 AmyvidT labeling Comments

Dear Mr. Truocchio,

I am covering for Ms. Sharon Thomas this afternoon. Please see the below information and please confirm receipt of this email.

NDA 202008

### **LABELING DISCUSSION COMMENTS**

Avid Radiopharmaceuticals, Inc.  
Attention: Stephen P. Truocchio, M.S., RAC  
Senior Director, Regulatory Affairs

Dear Mr. Truocchio:

Please refer to your October 7, 2011 New Drug Application (NDA) resubmission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir f 18) Injection.

On March 12, 2012, we received your revised proposed labeling submission to the non clinical sections of this application, and have proposed clinical revisions that have been reviewed and cleared to the level of Office Director. Please supply a response to the following by e-mail to my attention [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB on **Wednesday, March 21, 2012:**

Attached here are our draft redline versions of the PI and container labels. Please examine the notes and comments/correct typographical and formatting errors and return a revised labeling proposal to your NDA as an amendment. Please justify altered text. Note that the yellow highlighted is intended solely to emphasize the "new" text that was not supplied last week/do not highlight text in the "clean copy" of your response.



FDAtoAvid3-16-201  
2bulk\_shield....



PI\_redlineFDAtoAvid  
d3-16-2012.d...

Thank you,  
Alberta

Alberta E. Davis-Warren  
Regulatory Health Project Manager  
Division of Medical Imaging Products

**From:** Thomas, Sharon  
**Sent:** Friday, March 09, 2012 10:55 AM  
**To:** 'Stephen Truocchio'  
**Cc:** Kristin White-Levine  
**Subject:** Labeling: CMC Comments /Information Requests - NDA 202008-Amyvid™ (florbetapir f 18) injection

NDA 202008

## LABELING DISCUSSION COMMENTS

Avid Radiopharmaceuticals, Inc.  
Attention: Stephen P. Truocchio, M.S., RAC  
Senior Director, Regulatory Affairs

Dear Mr. Truocchio:

Please refer to your October 7, 2011 New Drug Application (NDA) resubmission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir f 18) injection. We have the following CMC Comments /Information Requests:

1. In the vial and shield container labels, as well as in the package insert revise the strength statement “ 37 – 1900 MBq (1 – 50 mCi) florbetapir F 18 at calibration” to “ 500 – 1900 MBq (13.5 – 51 mCi) florbetapir F 18 at End of Synthesis (EOS) calibration”.
2. Clarify if the actual “Contract Manufacturing Organization” will be specified in the actual label used by each manufacturer.

Please supply a response to the following by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB on **Wednesday, March 14, 2012.**

If you have any questions, please feel free to contact me.

Thank you,

Sharon

\*\*\*\*\*  
Sharon P. Thomas  
Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV - CDER - FDA

Phone: 301-796-1994  
Fax: 301: 796-9849  
[sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

**From:** Thomas, Sharon  
**Sent:** Friday, March 09, 2012 9:37 AM  
**To:** 'Stephen Truocchio'  
**Cc:** Kristin White-Levine  
**Subject:** FDA- Labeling- NDA 202008- Amyvid™ (florbetapir f 18) injection

NDA 202008

## **LABELING DISCUSSION COMMENTS**

Avid Radiopharmaceuticals, Inc.  
Attention: Stephen P. Truocchio, M.S., RAC  
Senior Director, Regulatory Affairs

Dear Mr. Truocchio:

Please refer to your October 7, 2011 New Drug Application (NDA) resubmission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir f 18) injection.

On December 19, 2011 and February 29, 2012, we received your revised proposed labeling submission to this application, and have proposed revisions that have been reviewed and cleared to the level of Division Director. Please supply a response to the following by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB on **Wednesday, March 14, 2012.**



FDAtoAvidParts3-9-FDAtoAvidParts3-9- ly2\_Amyvid Vial  
2012Clean.do... 2012RedLine.... -ShieldLabel3-...

If you have any questions, please feel free to contact me.

Thank you,

Sharon Thomas, RPM  
Division of Medical Imaging Products  
ODE IV/ CDER/ FDA  
(301) 796-1994 (office)  
(301) 796-9849 (fax)

**From:** Thomas, Sharon  
**Sent:** Tuesday, February 21, 2012 5:01 PM  
**To:** 'Stephen Truocchio'  
**Cc:** David Haenick; Kristin White-Levine  
**Subject:** Information Request- NDA 202008- Amyvid

NDA 202008

## INFORMATION REQUEST

Avid Radiopharmaceuticals, Inc.  
Stephen P. Truocchio, M.S., RAC  
Senior Director, Regulatory Affairs

Dear Mr. Truocchio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid (Florbetapir F 18) Injection. We are currently reviewing your proposed labeling in the context of the information supplied to the NDA. Please supply a response to the following inquiring within five business days.

- The technical report number TR-AV-45-085 states that [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] The report summarizes the data that supported this conclusion. The proposed labeling does not address these infusion considerations. Justify the exclusion of the TR-AV-085 main conclusions from your drug's proposed labeling; alternatively, submit revised labeling that addresses the RV-AV-085 findings. If revised labeling is proposed, the text should describe the infusion limitations in a clinically-applicable manner [REDACTED] (b) (4)  
[REDACTED]

In the interest of time, please first provide a response by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB on Tuesday, February 28, 2012, and then follow up with an amendment to the NDA. If you have any questions, please feel free to contact me.

Thank you,

*Sharon*

Sharon Thomas, RPM  
Division of Medical Imaging Products  
Office of Drug Evaluation IV, CDER, FDA  
Phone: (301) 796-1994  
Fax: (301) 796-9849  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Tuesday, December 13, 2011 5:16 PM  
**To:** 'Stephen Trucchio'  
**Cc:** Alan Carpenter  
**Subject:** RE: NDA 202-008 Information Request  
**Attachments:** 202008AmyvidInformation Request121311.pdf

Dear Stephen,

Attached is an Information Request for Amyvid from the Division. Please provide a formal response to the NDA (and a WORD version of the label to me via email) by Dec. 27th.

Should you have any questions, please don't hesitate to contact me.

Best regards,  
Sharon

---

**From:** Thomas, Sharon  
**Sent:** Wednesday, November 30, 2011 2:08 PM  
**To:** Stephen Truocchio  
**Cc:** 'Alan Carpenter'; Kristin White-Levine  
**Subject:** NDA 202-008 Amyvid

Hi Steve,

Please re-submit the pediatric plan / waiver request for Amyvid under the NDA.

Here is the link to the Guidance for Industry document regarding How to comply with the Pediatric Research Equity Act:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>

and from the legislation:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>

“(a) NEW DRUGS AND BIOLOGICAL PRODUCTS.—

“(1) IN GENERAL.—A person that submits, on or after the date of the enactment of the Pediatric Research Equity Act of 2007, an application (or supplement to an application)—

“(A) under section 505 for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, or “(B) under section 351 of the Public Health Service Act (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, shall submit with the application the assessments described in paragraph (2).

“(2) ASSESSMENTS.—

“(A) IN GENERAL.—The assessments referred to in paragraph

(1) shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate—

“(i) to assess the safety and effectiveness

Please let me know if you have any questions. Thanks.

R/

Sharon



pedwaiver.pdf (92 KB)



IND 79511 Serial  
69\_revised 3 ...

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Monday, November 07, 2011 8:22 AM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine; Stephen Truocchio; David Haenick  
**Subject:** RE: Teleconference- Thurs. 11/10/11  
**Attachments:** N202008ClinStatInformation Request110611 (2).pdf

Hi Dr. Carpenter,

Attached is the Clinical /Statistical Information Request which will serve as the basis for discussion for Thursday's teleconference.

We would like a written response by COB on Wed., 11/9/11 ( preferably no later than 7 calendar days).

Please don't hesitate to contact me if you have any questions.

Thank you,  
Sharon Thomas, RPM

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**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Thursday, November 03, 2011 9:54 PM  
**To:** Thomas, Sharon  
**Cc:** Kristin White-Levine; Stephen Truocchio; David Haenick  
**Subject:** RE: Teleconference- Thurs. 11/10/11

Dear Ms. Thomas,

Can you please let us know the subject of the discussions? We just want to make sure we have the correct (Clinical or CMC) people available for the call.

Thank you,

Alan Carpenter

Alan P. Carpenter, Jr., Ph.D., J.D.  
Vice President, Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7<sup>th</sup> floor  
Philadelphia, PA 19104  
215-298-0707  
857-928-4520 (mobile)  
[carpenter@avidrp.com](mailto:carpenter@avidrp.com)

**From:** Thomas, Sharon [mailto:Sharon.Thomas@fda.hhs.gov]  
**Sent:** Thursday, November 03, 2011 5:59 PM  
**To:** Alan Carpenter  
**Cc:** Kristin White-Levine; Stephen Truocchio; David Haenick  
**Subject:** Teleconference- Thurs. 11/10/11

Hi Dr. Carpenter,

The Division would like to speak with Avid on Thursday, 11/10/11 at 10:40 AM to discuss some issues concerning the NDA resubmission for Amyvid. I will forward an information request/comments on Monday, 11/7/11 by COB.

Please confirm your availability.

**Teleconference:**

**Thursday, November 10, 2011 at 10:40 AM**

**Dial in Details:**

**1-866-692-4541**

**Participant Passcode:** (b) (4)

Best regards,

Sharon Thomas, RPM  
Division of Medical Imaging Products  
ODE IV/ CDER/ FDA  
(301) 796-1994 (o)

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Thursday, October 06, 2011 8:13 PM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** RE: IND 79511 (sn 129) - Clinical Information Request  
**Attachments:** Clin79511Advice-Information Reques10-6-11 (2).pdf

Dear Dr. Carpenter,

Attached is a Clinical Information Request for Florbetapir F18 in response to your Sept. 6<sup>th</sup> protocol submission.

Please feel free to contact me should you have any questions.

Thank you,  
Sharon Thomas, RPM

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Friday, September 16, 2011 2:02 PM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** RE: Confirmation of October 11 Meeting

Dr. Carpenter,

Per our discussion, I would like to confirm Oct. 11<sup>th</sup> from 11:30 -1pm at our White Oak facility in Silver Spring. Thank you for bringing the laptop that will include the meeting presentation and web-based training materials. Please send me Avid's list of attendees to clear security.

I will follow up if the team has any information requests prior to the meeting.

Best regards,  
Sharon

---

**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Friday, September 16, 2011 12:35 PM  
**To:** Thomas, Sharon  
**Cc:** Kristin White-Levine  
**Subject:** Confirmation of October 11 Meeting

Dear Ms. Thomas,

Thank you for the call yesterday afternoon. I can now confirm that Avid will be available to present an overview/orientation to the completed NDA resubmission for Amyvid on October 11 from 11am to 12:30pm. We will bring the presentation on a laptop to the meeting as suggested.

Sincerely,

Alan Carpenter

Alan P. Carpenter Jr., Ph.D., J.D.  
Vice President, Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th floor  
Philadelphia, PA 19104  
215-298-0707  
857-928-4520 (mobile)  
carpenter@avidrp.com

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Thursday, September 01, 2011 9:24 AM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** RE: Avid responses to FDA Advice/Information Request of 8-29-11

Dr. Carpenter,

After further discussion, the Division would like to cancel today's t-con. Please formally submit the amended protocol and responses to the Advice letter to IND 79511.

Thank you,  
Sharon

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**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Wednesday, August 31, 2011 12:08 PM  
**To:** Thomas, Sharon  
**Cc:** Kristin White-Levine  
**Subject:** Avid responses to FDA Advice/Information Request of 8-29-11

Dear Ms. Thomas,

Attached are a letter to Dr Rieves and the Division with Avid's responses to the Advice/Information Request received from DMIP on 8-29-11. Also attached is a draft amendment to the 18F-AV-45-PT01 study protocol which incorporates all of the requests of the Agency in the 8-29 Advice Letter.

Since we have incorporated all requests of the FDA into this protocol amendment Avid does not feel the need for additional clarification discussions via teleconference on September 1. Following review of our written responses and the draft protocol amendment, if the Division agrees then Avid will submit this protocol amendment to IND 79,511 and complete the study with the incorporation of the Division's recommendations as provided in the 8-29 letter.

Please let me know if Dr Rieves and the Division still feel a teleconference is needed.

Sincerely,

Alan Carpenter

Alan P. Carpenter Jr., Ph.D., J.D.  
Vice President, Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th floor  
Philadelphia, PA 19104  
215-298-0707  
857-928-4520 (mobile)  
carpenter@avidrp.com

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Monday, August 29, 2011 11:48 AM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine; David Haenick  
**Subject:** RE: Teleconference- Thurs. 9/1/11  
**Attachments:** 79511Advice-Information Request.pdf

Dear Dr. Carpenter,

Please find attached the Division's comments that will serve as the basis for discussion for the Sept. 1<sup>st</sup> teleconference. If possible, please provide written responses via email on Wed. Aug. 31<sup>st</sup>.

Please feel free to contact me if you have any questions.

Sharon Thomas, RPM  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA  
301-796-1994 (office)

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**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Thursday, August 25, 2011 9:07 AM  
**To:** Thomas, Sharon  
**Cc:** Kristin White-Levine; David Haenick  
**Subject:** RE: Teleconference- Thurs. 9/1/11

Dear Ms. Thomas,

Thank you for the meeting notice. I am confirming our availability for this teleconference for September 1 at 1:15PM.

Sincerely,

Alan Carpenter

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Alan P. Carpenter, Jr., Ph.D., J.D.  
Vice President, Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104  
phone: (215) 298-0707  
cell: (857) 928-4520  
[www.avidrp.com](http://www.avidrp.com)  
[carpenter@avidrp.com](mailto:carpenter@avidrp.com)

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**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Tuesday, August 23, 2011 11:41 PM  
**To:** 'Alan Carpenter'  
**Cc:** David Haenick; Kristin White-Levine  
**Subject:** RE: Update from Avid regarding Amyvid (Florbetapir F 18 Injection)

Thank you, Dr. Carpenter.

The Division would like to discuss your amendment ( IND 79511 sn# 124) on next week. I will forward an information request/comments via email on Thursday and submit t-con details by COB on tomorrow.

Best regards,

Sharon Thomas, RPM  
Division of Medical Imaging Products  
ODE IV/ CDER/ FDA  
(301) 796-1994 (o)

---

**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Tuesday, August 23, 2011 9:13 AM  
**To:** Thomas, Sharon  
**Cc:** David Haenick; Kristin White-Levine  
**Subject:** Update from Avid regarding Amyvid (Florbetapir F 18 Injection)

Dear Ms. Thomas,

I wanted to provide you and DMIP a brief update on the status of our work leading up to a resubmission in response to the FDA Complete Response Letter of March 17 this year. Following our multiple discussions culminating in the teleconference on June 14 related to the reader training study, we have submitted the final protocol and statistical justification document to the IND (#79,511, amendment 0124, dated August 8, 2011). Avid is now in the process of conducting this study of web-based (not-in-person) reader training. We expect this study to be completed, along with all responses to the CRL, for the NDA resubmission (if the study meets its goals) by approximately September 30. We will confirm our expected resubmission date with you when we are within a week of submission.

I also wanted you and the ONDPQ CMC reviewers to know that Avid submitted a substantial response to the Philadelphia District Office form 483 observations on August 1 (copy attached for your information). A further revision to the response was submitted by email on August 22 (attached), and we expect to complete our responses to requests of DMPQ at CDER related to manufacturing site qualifications over the next month. Therefore, it is our goal to address all outstanding requests of the various CDER reviews by the end of September. We will keep you abreast of any further developments or changes to the status of the Amyvid NDA resubmission plans over the near future.

Sincerely,

Alan Carpenter

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Tuesday, June 14, 2011 8:25 AM  
**To:** 'Alan Carpenter'  
**Subject:** RE: FDA Comments (Reader Training Program)- Today's t-con

Dr. Carpenter,

Thank you for Avid's comments regarding our information requests/comments sent on Friday, June 10, which will serve as the basis for today's discussion. Please forward your list of participants and I have re-submitted the dial in details below. Below are the FDA's attendees.....some may dial in.

Charles Ganley, M.D., Director, ODE IV  
Shaw Chen, M.D., Deputy Director, ODE IV  
Rafel Rieves, M.D., Director, DMIP  
Louis Marzella, M.D., Ph.D., Deputy Division Director, DMIP  
Alex Gorovets, M.D., Clinical Team Leader, DMIP  
Qi Feng, M.D., Primary Clinical Reviewer, DMIP  
Lucie Yang, M.D., Ph.D., Clinical Team Leader, DMIP  
Anthony Mucci, Ph.D., Statistical Team Leader, D  
Lan Huang, Ph.D., Statistical Reviewer, DBI  
Thomas Gwise, Ph.D., Statistical Reviewer  
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP  
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, OCP

**Dial in Details:**

1-866-692-4541

Participant Passcode: (b) (4)

Please don't hesitate to contact me if you have any questions.

Thank you,  
Sharon Thomas, RPM

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**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Monday, June 13, 2011 12:15 PM  
**To:** Thomas, Sharon  
**Cc:** Kristin White-Levine  
**Subject:** RE: FDA Comments (Reader Training Program)

Dear Ms. Thomas,

Please find attached Avid's preliminary responses to the FDA Advice/Information Request of 6/10/11.

We look forward to our teleconference discussion tomorrow at 11am.

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Friday, June 10, 2011 4:42 PM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** RE: FDA Comments (Reader Training Program)  
**Attachments:** Clin79511Advice-Information Request6-10-11.pdf

Dear Dr. Carpenter,

Attached are FDA comments/information requests regarding your April 27th submission.

The Division will proceed with the teleconference scheduled for Tuesday, June 14, 11:00 am-12:00 pm. Please don't hesitate to contact me if you have any questions.

**Dial in Details:**

1-866-692-4541

Participant Passcode: (b) (4)

**Thomas, Sharon**

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**Subject:** FW: IND 79511 sn 0120, Florbetapir Reader Training Materials

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**From:** Thomas, Sharon  
**Sent:** Thursday, May 19, 2011 1:18 PM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine; Michael Krautkramer; Miller, Kimberly D.  
**Subject:** RE: IND 79511 sn 0120, Florbetapir Reader Training Materials

Dr. Carpenter,

Please direct the courier to contact our Project Specialist, Kim Miller.

Thank you,  
Sharon Thomas

**Kim Miller/ OND/ODEIV/DMIP**  
**WO22 RM5247 HFD-160**  
**10903 New Hampshire**  
**Direct # (301) 796- (b) (6)**

---

**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Thursday, May 19, 2011 12:04 PM  
**To:** Thomas, Sharon  
**Cc:** Kristin White-Levine; Michael Krautkramer  
**Subject:** RE: IND 79511 sn 0120, Florbetapir Reader Training Materials

Dear Ms. Thomas,

I am writing to confirm that a courier for Avid will be delivering the laptop loaded with the reader training program materials for Amyvid, which the Division expects to receive today. The name of the courier is (b) (6) (no kidding!), and the expected time of arrival at White Oak, barring any major traffic problems, is between 2:00 and 3:00pm this afternoon. There are written instructions included along with the laptop, but I am also attaching a copy here to make sure you have a copy to distribute to whoever needs them. Avid is also prepared to formally submit these materials to the IND, following agreement from you on how best to do this following our conference call on June 2<sup>nd</sup>.

Please do not hesitate to call us if there are any questions from the reviewers regarding how to review the materials we have sent.

Sincerely,

Alan Carpenter

P.S. If you expect to send us any written comments or recommendations from the review team on the protocol or training materials prior to the June 2<sup>nd</sup> teleconference would you please copy all of the individuals above, since some of us may be away around the holiday weekend. Thank you very much.

---

**From:** Thomas, Sharon  
**Sent:** Friday, May 13, 2011 2:24 PM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** FW: IND 79511 sn 0120, Florbetapir Reader Training Materials

Hi Dr. Carpenter,

The Division has agreed with Avid's proposal to review the draft reader training program on your laptop to be submitted on Thurs., May 19th. Please choose a firm /courier in Silver Spring, MD to the deliver the materials to:

Food and Drug Administration/ White Oak  
Attention: Sharon Thomas, RPM  
10903 New Hampshire Avenue  
Bldg. 22, Room 5231  
Silver Spring, MD 20993

(301) 796-1994 (Direct #)  
(301) 796- (b) (6) (Kim Miller- Project Specialists)

Let me know if you have any further questions.

Thank you,  
Sharon Thomas, RPM

---

**From:** Thomas, Sharon  
**Sent:** Wednesday, May 11, 2011 4:32 PM  
**To:** 'Alan Carpenter'  
**Subject:** IND 79511 sn 0120

Dear Dr. Carpenter,

Please find enclosed a clinical information request for florbetapir F18. Should you have any questions please don't hesitate to contact me.



Clinical79511Advice  
-Informatio...

Thank you,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Tuesday, May 03, 2011 4:44 PM  
**To:** 'Alan Carpenter'  
**Cc:** John Lister-James; Kristin White-Levine; Karen Marshall  
**Subject:** RE: Avid Radiopharmaceuticals 483 Response/ T-con

Dr. Carpenter,

Thank you very much for your email. I will follow-up with Dr. Kasliwal and our Compliance Team regarding the submission.

The Division would like to discuss your Reader Training Program on 6/2/11. We have an internal meeting scheduled on 5/26/11 and we will probably forward comments/information requests after the meeting.

Please confirm your availability. I have provided the dial in details below.

Thank you,  
Sharon Thomas, RPM

**Teleconference**

Thurs., June 2, 2011 12:30 pm - 1:30 pm

**Dial in details**

1-866-692-4541

**Participant Passcode:** (b) (4)

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**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Tuesday, May 03, 2011 12:32 PM  
**To:** Thomas, Sharon  
**Cc:** John Lister-James; Kristin White-Levine; Karen Marshall  
**Subject:** FW: Avid Radiopharmaceuticals 483 Response

Dear Ms. Thomas,

In follow-up to the attached email, John Lister-James, our VP of Chemical Development and Manufacturing, would like to know if Dr. Kasliwal has had the opportunity to review this 483 response, which Avid submitted to the Philadelphia District office last month. Since Dr. Kasliwal is the primary CMC reviewer for Florbetapir F 18 Injection (18F-AV-45), we wanted to know if he has any comments or concerns about this response to the field office. If he feels that a phone discussion would be needed to discuss this matter we would be happy to do so.

Sincerely,

Alan Carpenter

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**From:** Thomas, Sharon  
**Sent:** Friday, March 18, 2011 9:07 AM  
**To:** 'Alan Carpenter'  
**Subject:** RE: Amyvid NDA 202-008- Teleconference -March 22, 2011- 1:30 pm - 2:00 pm

Good morning Dr. Carpenter,

Please see the dial in details below.

Thank you,  
Sharon Thomas, RPM

**1-866-692-4541**

**Participant Passcode:** (b) (4)

**From:** Alan Carpenter  
**Sent:** Thursday, March 17, 2011 5:13 PM  
**To:** 'Thomas, Sharon'  
**Subject:** RE: Amyvid NDA 202-008

Dear Ms. Thomas,

Thank you for your call. As requested, I am confirming receipt of the CR Letter for NDA 202-008 and also our availability to have a conference call with the Division to discuss this letter on next Tuesday March 22 at 1:30pm.

Sincerely,

Alan Carpenter

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Alan P. Carpenter, Jr., Ph.D., J.D.  
Vice President, Legal & Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104  
phone: (215) 298-0707  
cell: (857) 928-4520  
[www.avidrp.com](http://www.avidrp.com)  
[carpenter@avidrp.com](mailto:carpenter@avidrp.com)

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/s/  
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SHARON P THOMAS  
03/26/2012

**DIVISION OF MEDICAL IMAGING PRODUCTS  
WRAP UP MEETING**

**DATE:** March 6, 2012

**TIME:** 1: 00 PM

**LOCATION:** Bldg 22,Room 1421

**APPLICATION:** NDA 202-008

**DRUG NAME:** AMYVID (florbetapir F 18) Injection

**SPONSOR:** Avid Radiopharmaceuticals

**FDA ATTENDEES:**

Sunday Awe, Ph.D., Pharm\Tox Reviewer

Laniyou, Adebayo, Ph.D., Pharm/Tox Team Leader

Gene Williams, Ph.D., Clinical Pharmacology Team Leader

Christy John, Ph.D., Clinical Pharmacology Reviewer

Qi Feng, M.D., Primary Clinical Reviewer

Alex Gorovets, M.D., Clinical Team Leader

Kevin Wright., OSE Project Manager

Anthony Mucci, Ph.D., Acting Statistical Team Leader

Rafel Dwaine Rieves, M.D., Division Director

Louis Marzella, M.D., Dep. Division Director

Sharon Thomas, Regulatory Health Project Manager

Lucie Yang, M.D., Ph.D., Clinical Reviewer

Jyoti Zalkikar, Ph.D., Statistical Team Leader

James Dvorsky, OMP/OPDP

**SUMMARY:** The team discussed the conclusions of the studies/information submitted by Avid. Cardinal Health in NC, GMP facility was issued a 483-citation.

**ACTION ITEM:** A possible Information Request will be forwarded from Micro.



**NDA 202008**

**INFORMATION REQUEST**

Avid Radiopharmaceuticals  
Attention: Alan P. Carpenter, Jr., PhD., J.D.  
Vice President, Regulatory Affairs  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your New Drug Application (NDA), class 2 resubmission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir f 18) injection.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products and have the following comments and information requests:

1. Revise the figures within your labeling to address the following items:
  - a. You include several black and white figures of brain sections (negative and positive results). We are having difficulty understanding the layout for Figures 2 and 3. Specifically, the Figure 2 legend says, “Typical Negative Scan (left).” We do not understand the purpose of the “left” denotation since the citation appears to indicate another figure is on the “right”; however, the “right” is blank. A similar question applies to Figure 3 (where there is a citation to “right”). Conceivably, the submitted pdf layout is not the representation you plan for marketing. Please supply a pdf document that contains the verbatim layout you plan for the prescribing information.
  - b. The Figure 2 and 3 legends refer to points A, B, C, and D in a manner that suggests these points should also be identified in the brain image; instead the supplied arrows on the images are not labeled as representative of points A, B, C, and D. We encourage you to revise the figures to include the labeled points within both the legend and the actual image.
  - c. We also encourage you to consider revising the figures to use lines (such as broken lines) to highlight the important brain anatomy landmarks (white matter, gray matter, perhaps CSF space, bone, etc).

2. The image interpretation section of your labeling does not describe the role of computerized tomography (CT) in image interpretation. Please consider revising the labeling to comment upon how readers are to use CT information, if available.
3. The training module appears to indicate that CT images were available for readers in Study PT01. Please clarify the extent, if any, to which CT images were available to the readers. If CT images were used in the reading sessions, then the labeling should describe the use of CT images.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

- **Contraindications:** If there are no contraindications, state “None” instead of (b) (4)
- **Revision Date:** A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of Highlights section. The revision date is the month/year of application or supplement approval.
- **Adverse Reactions:** For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- **Picture size:** Please review and confirm the size of the pictures in the labeling. They are acceptable for the SPL as long as the JPEG files are less than 1 MB in size.

We request that you resubmit labeling that addresses these issues by December 27, 2011. The resubmitted labeling will be used for further labeling discussions.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Rafel Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV (ODE IV)  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAFEL D RIEVES  
12/13/2011

## TELECON MINUTES

**TELECON DATE:** 11/10/11 **TIME:** 11:15AM- 11:45 AM **LOCATION:** Room 2327

**NDA:** 202-008 **DRUG:** Amyvid™ (florbetapir F 18) Injection

**SPONSOR/APPLICANT:** Avid Radiopharmaceuticals

**TYPE of TELECON:** Discuss/clarify the location of items in the NDA re-submission.

### FDA PARTICIPANTS:

Rafel Rieves, MD, Division Director, DMIP (*Meeting Chair*)  
Louis Marzella, MD, PhD – Deputy, Division Director, DMIP  
Lucie Yang, MD, PhD- Acting, Team Leader (TL), DMIP  
Qi Feng, MD, PhD- Primary Clinical Reviewer, DMIP  
Anthony Mucci, PhD- Statistical Team Leader, DBV  
Lan Huang, PhD- Statistical Reviewer, DBV  
Jyoti Zalkikar, PhD- Statistical Supervisor, DBV  
Sharon Thomas, Regulatory Project Manager, DMIP (*Meeting Recorder*)

### INDUSTRY PARTICIPANTS:

Mark Mintun, M.D., Chief Medical Officer  
Daniel Skovronsky, MD, PhD, CEO  
Michael Pontecorvo, PhD, VP, Clinical Development  
Christopher Clark, MD, Medical Director  
Ming Lu, PhD, Lead Statistician  
Michael Krautkramer, MBA, VP, Operations  
Stephen Truocchio, MS, Senior Director, Regulatory Affairs  
Alan Carpenter, PhD, VP, Regulatory Affairs

Deleted: ¶

### BACKGROUND:

On November 3, 2011, FDA requested a teleconference to discuss or clarify missing items in the NDA re-submission. Avid agreed to the teleconference on November 4, 2011. On November 7, 2011, FDA submitted comments in an Information Requests letter to serve as the basis for discussion. On November 9, 2011, Avid provided draft responses. FDA comments are in bold font followed by Avid's draft responses in regular font. The discussion points are indicated in *bold italics* below.

### FDA Comment #1

**According to your proposed label in the October 7, 2011 NDA resubmission, section 6.1, the total number of subjects administered florbetapir in clinical trials totaled “N=496 patients” (520 administrations). We note that this is the same number of subjects and florbetapir administrations stated in section 6.1 of the label submitted on September 17,**

**2010 in your original NDA. Based on Module 2.7.4 of Amendment 018, we are aware of at least 3 subjects who were administered florbetapir between the date of your original NDA submission (September 17, 2010) and your NDA resubmission (October 7, 2011).**

- a. **Clarify the total number of the subjects administered florbetapir between September 17, 2010 and October 7, 2011. As described in our letter of March 17, 2011, updated exposure information is important to the safety assessment for your drug. If more than 496 subjects have been exposed to your drug, you will need to revise your safety information submission, as outlined below.**

Avid's Draft Response to FDA's Comment #1a - E-mail dated November 9, 2011

The table below provides the total exposure to florbetapir in Avid-sponsored studies through 29 September 2011; including nine ongoing studies of florbetapir. A similar table showing total exposure to Amyvid in Avid-sponsored studies was included in Module 1.2 (Reviewer Guide), Section 2, Narrative Response to the Complete Response Letter, of the NDA Resubmission

Table 1: Subject Exposure in Avid-Sponsored Clinical Studies

Study number	Location	Number of Subjects Exposed	Safety Data Included in NDA and Resubmission
<b>Completed Studies</b>			
A01	US	32	All
A02	US	9	All
A03	US	20	All
A04	US	25	All
A05	US	184	All
A07	US	226	All
	Total completed:	496	
<b>Ongoing studies (Avid-monitored studies)</b>			
A11	US	86 <sup>a</sup>	SAEs only
A12	US	27	SAEs only
A14	US	203	SAEs only
A17	US	2 <sup>c</sup>	SAEs only
ACRIN 1403	US	27	SAEs only
010	UK	10	SAEs only
AV-133-B03 <sup>b</sup>	US	31	SAEs only
<b>Ongoing studies (NIA/ADCS-monitored studies)</b>			
A15-ADNI-GO	US/Canada	268	SAEs only
ADNI-2	US	137	SAEs only
	Total ongoing:	791	
	<b>Completed plus Ongoing Total</b>	<b>1287</b>	

NIA/ADCS=National Institute on Aging/Alzheimer's Disease Cooperative Study.

- <sup>a</sup>. All subjects in Study A11 were previously dosed with florbetapir in Study A05 and received a second florbetapir scan 24 months after the initial A05 scan.
- <sup>b</sup>. Avid Study AV-133-B03 is being conducted under IND (b)(4). Subjects receive scans using AV-133 and AV-45 (florbetapir)
- <sup>c</sup>. Not currently enrolling subjects, pending protocol amendment

As of 29 September 2011, in addition to the 1287 subject exposures described above, there have been 1001 subjects exposed to florbetapir in ongoing studies using florbetapir as a biomarker in support of investigational therapeutics under INDs sponsored by other companies. In addition, 290 subjects have been exposed to florbetapir in investigator-sponsored studies (not sponsored by Avid) conducted outside of the United States (in Taiwan, France, and Japan).

The Module 2.7.4 Addendum will be revised to include this updated exposure information.

- ***DISCUSSION POINT # 1a:***  
***FDA acknowledged the location of the subject exposures included in Module 1.2 in the Reviewers Guide.***
- b. Modify section 6.1 of the draft label to account for the adverse reactions experienced by all subjects administered florbetapir prior to the date of your NDA resubmission (October 7, 2011). If there are other sections of the label that require revision based on the subjects administered florbetapir between September 17, 2010 and October 7, 2011, please update these sections before providing the updated draft label to FDA. Supply the revised safety sections of your submission to support your altered labeling.**

Avid's Draft Response to FDA's Comment #1b - E-mail dated November 9, 2011

The PI and 2.7.4 Summary of Clinical Safety and 2.7.4 Addendum (NDA Amendment serial number 018) contain all adverse events from completed Avid-sponsored studies and all SAEs reported from all completed and ongoing studies as of the designated cutoff of 29 September 2011. Since there were no SAEs related to florbetapir, there is no discussion of SAEs in the proposed PI. Does the agency agree with this approach?

- ***DISCUSSION POINT # 1b:***  
***FDA concurred. There was no further discussion.***
- c. Provide an updated Integrated Summary of Safety (Module 5.3.5.3 in accordance with 21 CFR 314.50(d)(5)(vi)) and Summary of Clinical Safety (Module 2.7.4 in accordance with 21 CFR 314.50(c)(2)(viii)) which accounts for all subjects administered florbetapir before October 7, 2011 (or the data cut-off period you have chosen for your submission). In general, the data cut-off period should, at a minimum, encompass the period of time during which any subjects experienced serious adverse events or other outcomes that you regard as important to the safety assessment for your drug.**

Avid's Draft Response to FDA's Comment 1c - E-mail dated November 9, 2011

SAEs from all studies are reported to Avid on an ongoing basis, and available SAEs with completed CIOMS forms were reported in the NDA 202-008 resubmission amendment serial number 018 (Module 2.7.4 Addendum). AEs and other safety data from ongoing, incomplete studies were not included. Quality-controlled safety data are not available for the ongoing studies. The three additional SAEs were reported in the Module 2.7.4 Addendum; however, they were not added to the SAE tabulations in Module 5.3.5.3. We note that in both the original NDA submission and NDA resubmissions, SAEs from ongoing studies were discussed only in the text portion of 2.7.4 and not included in the 5.3.5.3 tabulations. If desired by the Agency, these tabulations in 5.3.5.3 can be modified to include these additional SAEs since the original NDA. Does the Agency suggest that we should modify 5.3.5.3 tabulations to include SAEs from the ongoing studies?

- **DISCUSSION POINT # 1c:**  
***FDA concurred with Avid's proposal to modify 5.3.5.3 tabulations to include SAEs from the ongoing studies.***

**FDA Comment #2**

**Provide a brief description of the responsibilities of the Clinical Research Organization (CRO) in study 18F-AV-45-PT01 (PT01), particularly as it applies to the process-flow of data from the readers to the primary endpoint dataset. Clarify if the source documents for study PT01 (documents that contain the reader-entered data) reside with the CRO, with Avid Radiopharmaceuticals, or with some other entity.**

Avid's Draft Response to FDA's Comment #2 - E-mail dated November 9, 2011

Two CROs were used in the conduct of Study PT01: (b)(4) and (b)(4). (b)(4) provided the randomization lists for renumbering the scans used in PT01. These new numbers determined the order of viewing the scans by the readers. (b)(4) designed the electronic CRF for Study PT01 and set up and hosted the database to capture the reader's scan interpretation results. (b)(4) provided the readers with their individual, unique login IDs and passwords to access the eCRF and enter their scan read results. The system was designed to prevent changing/altering of the data by unauthorized persons. Readers were not able to see other reader results. After all reads were completed, the data were then transferred to Avid and (b)(4) for statistical analyses. Avid created the analysis datasets submitted in the NDA resubmission and the statistical tables, figures, and listings contained in PT01 study report. The results of statistical analyses were independently verified by (b)(4).

Reader-entered data were collected directly on the eCRF; therefore, the source data for the reader-entered scan interpretations resides in the database available at (b)(4).

- **DISCUSSION POINT # 2:**  
***Avid confirmed that (b)(4) has an electronic database system only. No paper CRFs. The database connects login information with specific readers and with eCRF answers.***

**FDA Comment #3**

**Submit or provide the location of the sample histopathology electronic Case Report Form (CRF) for the PT01 study. We note that you have supplied the sample case report form for the imaging aspect (section 16.1.2 of the clinical study report). However, we need to see the CRF the pathologists completed in order to help verify the data integrity.**

Avid's Draft Response to FDA's Comment #3 - E-mail dated November 9, 2011

The sample pathology CRFs for the autopsy data are included in Study A16 Appendix 16.1.9:

-The plaque counts (Bielschowsky Data Collection Form) is on page 40

-The Neuropathology Diagnosis Form is on page 41

-An example of the automated Immunohistochemistry process output is on page 33

o **DISCUSSION POINT # 3:**

*Avid confirmed the location of the CRF in 16.1.10.*

**FDA Comment #4**

**Submit or identify the location of the raw (source) datasets (xpt files) for the PT01, 18FAV 45-A16 (A16), 18F-AV-45-A09 (A09), and 18F-AV-45-A08 (A08) studies, including the define.pdf. Submit or identify the location of the analysis datasets (xpt files) for the A16, A09, and A08 studies.**

Avid's Draft Response to FDA's Comment #4 - E-mail dated November 9, 2011

Analysis datasets in xpt format for PT01 were provided in the NDA resubmission serial 0018 (PT01 define.pdf). Raw datasets will be provided as xpt files for PT01, A16, A09, and A08 in an NDA amendment (as soon as possible subject to the FDA teleconference discussions to be held on 10 November). Analysis datasets for A16, A09, and A08 will also be provided as xpt files, in this same planned NDA amendment.

o **DISCUSSION POINT # 4:**

*Avid agreed to submit datasets for A16, A09, and A08 as .xpt files as an NDA amendment.*

**FDA Comment #5**

**Submit or identify the location of the results for subgroup analyses (e.g., analyses by gender, age, racial and others) for study PT01.**

Avid's Draft Response to FDA's Comment #5 - E-mail dated November 9, 2011

There are no new scans being evaluated in the NDA resubmission. The original NDA provided an analysis of the full integrated scan dataset using quantitative SUVR results to compare results in various subgroups (2.7.3 Summary of Clinical Efficacy Table 29). In response to the specific request, Table 2 below is a summary of the reader performance results by subject subgroup for study PT01. As can be seen in the table, most subgroups are small and confidence intervals are wide. No meaningful differences between subgroups are observed for inter-reader reliability or reader performance in this study.

Does the agency request submission of this analysis as an NDA amendment?

Table 2: Subgroup Analysis of Inter-Reader Reliability and Reader Performance in Study PT01

Sub-Group	Kappa (95% CI) N=151)	Sensitivity <sup>a</sup> (95% CI) (N=39)	Specificity <sup>a</sup> (95% CI) (N=20)	Accuracy <sup>a</sup> (95% CI) (N=59)
<b>Gender</b>				
Male	0.81 (0.74, 0.88) n=76	76% (53%, 90%) 13/17	100% (76%, 100%) 12/12	86% (69%, 95%) 25/29
Female	0.85 (0.78, 0.92) n=75	95% (78%, 99%) 21/22	88% (53%, 98%) 7/8	93% (79%, 98%) 28/30
<b>Age</b>				
< 65	0.92 (0.82, 1) n=34	75% (30%, 95%) 3/4	100% (57%, 100%) 5/5	89% (57%, 98%) 8/9
>=65	0.81 (0.75, 0.86) n=117	89% (74%, 96%) 31/35	93% (70%, 99%) 14/15	90% (78%, 96%) 45/50
<b>Race</b>				
Caucasian	0.83 (0.78, 0.88) n=141	86% (72%, 94%) 32/37	94% (74%, 99%) 17/18	89% (78%, 95%) 45/59
Non-Caucasian	0.91 (0.71, 1) n=10	100% (34%, 100%) 2/2	100% (34%, 100%) 2/2	100% (51%, 100%) 4/4

CI=confidence interval

<sup>a</sup> based on the majority read.

- ***DISCUSSION POINT # 5:***  
***FDA asked Avid to submit the above analysis as an NDA amendment. Avid concurred.***

#### **FDA Comment #6**

**Submit or identify the location of the safety data (xpt files with define.pdf) with any updated information after the original submission (as mentioned above).**

Avid's Draft Response to FDA's Comment #6 - E-mail dated November 9, 2011

Avid agrees to provide updated datasets in accordance with the plans outlined in the response to question 1c.

- ***DISCUSSION POINT # 6:***  
***FDA agreed with Avid's proposal to provide updated datasets.***

**FDA Comment #7**

**Within the electronic Case Report Tabulation (CRT) designated as Study AV45PT01 - ADSL (Module 5.3.5.3.25.3.1):**

- a. **Please clarify the development of the outcome variable, “HIGHNEUR”—which we understand to represent the highest neuritic plaque count for a subject’s brain and apparently the main determiner of amyloid positivity/negativity. Describe how this number is developed for each subject and how the number differs from the “total plaque burden” (page 19 of 45/Neuropathology Analysis Protocol) and the “average regional plaque level” cited in the 18F-AV-45-A07 (A07) study report. Does the highest neuritic plaque count include both diffuse and neuritic plaques? Cite the appropriate documents that describe the composition of the amyloid plaque score that forms the standard of truth.**

Avid’s Draft Response to FDA’s Comment #7a - E-mail dated November 9, 2011

For modified CERAD Diagnosis (sensitivity/specificity analysis):

The expert neuropathologist’s modified CERAD diagnosis was the sole, final determiner of amyloid positivity/negativity. The neuropathologist made this diagnosis based on a review of tissue slides from three diagnostic regions (Middle Frontal Gyrus, Middle Temporal Gyrus, and Hippocampus) along with the reported highest neuritic plaque counts from those slides (based on two independent technologist’s measurements) and rendered the appropriate final CERAD neuropathologic diagnosis (pg 19 of A07 Neuropathology analysis protocol). Of the three slides reviewed by the pathologist, ‘HIGHNEUR’ represents the highest neuritic plaque count of the set. The key documents describing the composition of the modified CERAD diagnosis that defines the standard of truth are the following:

For Study A07

- Pg 19 -20 of A07 Neuropathology Analysis Protocol
- Cited article: Bennett DA et al, Neurology 2005
- Study A07 SAP, Appendix 3. Algorithm for modified CERAD Diagnosis

For Study A16

- pg 19 of A16 Neuropathology Analysis Protocol, Table 2
- Cited article: Bennett, DA et al, Neurology 2005
- Study A16 SAP, Section 6.4.4 Table 4

For measurement of total brain neuritic  $\beta$ -amyloid (correlation analysis):

‘Total plaque burden’ was not a variable used in any analyses. The term ‘total plaque burden’ used in the Neuropathology Analysis Protocol (pg 19 of A07 Neuropathology Analysis Protocol) is a descriptor for the semi-quantitative scale (CERAD: none, sparse, moderate, or frequent) used to categorize plaque counts. The plaque counts were used to calculate average regional plaque levels and global plaque levels as described in the SAP Section 6.4.4 (A07 & A16). Diffuse plaque counts were not used in any analyses in studies A07 or A16.

Thus, the term ‘total plaque burden’ defined a process step and was not an analysis variable; while ‘HIGHNEUR’ is a specific outcome variable which came from the three regions evaluated to determine the modified CERAD diagnosis.

**b. Within the outcome variable of “IHC”, are the reported numbers in “% of brain”?**

Avid’s Draft Response to FDA’s Comment #7a - E-mail dated November 9, 2011

The values from the IHC outcome variable are reported as the percent area of  $\beta$ -amyloid staining in the grey matter of a tissue sample slide (or set of slides). In studies A07 and A16, the average of all the IHC tissue sample slides in a region is reported as the Measurement of Cortical Burden by Region (%) and the average of the regional IHC values is reported as the Average Cortical Amyloid Burden (%).

o **DISCUSSION POINT # 7:**

*FDA asked whether the SOT outcome differed between A07 and PT01. Avid explained that the A07 had two primary endpoints; correlation based on IHC measurements and neuritic plaque counts. The SOT for PT01 (identical to that for A16) was based upon the diagnosis rendered by the pathologist. FDA inquired about the highest neuritic plaque count in the analytical dataset, if it was the ultimate determiner of the modified CERAD score. Avid responded that the ultimate determiner was the neuro pathologist that reviewed the slide with the number associated with the highest neuritic plaque count to categorize it as sparse, non sparse, moderate or frequent. FDA expressed concern about the inability to duplicate analysis due to the inconsistent naming of truth standard outcome variables among different documents in the NDA submission and with respect to previously submitted documents. FDA encouraged Avid to develop a data dictionary that would include terms and descriptors to explain the variables. FDA asked Avid to use or cross reference the same terminology in the protocol, clinical study report and SAP. Avid concurred. FDA asked if the histopathology results from subjects in A07 were read a second time for A16 or if the results taken from the A07 study. Avid explained that the pathology results for subjects included in both A07 and A16 were not read a second time. The same pathologist used the same algorithm to continue reading the next 24 autopsies.*

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no unresolved issues.

**ACTION ITEMS:**

- 1) Avid to revise Module 2.7.4 to include the exposure information.
- 2) Avid to modify 5.3.5.3 tabulations to include SAEs from the ongoing studies.

- 3) Avid to provide raw and analysis datasets for PT01, A16, A09, and A08 in .xpt files with define.pdf files.
- 4) Avid to submit the reader performance results by subgroups for study PT01 outlined above in Table 2.
- 5) Avid to submit an amendment to include a concise explanation of the SOT determination and a data dictionary, particularly for variables included in the primary endpoint analytical dataset for PT01.

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/s/  
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SHARON P THOMAS  
11/16/2011



NDA 202-008

**INFORMATION REQUEST**

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir F 18) Injection.

We refer you to your October 7, 2011 submission to NDA 202008 (Amendment 018, NDA resubmission) and your September 17, 2010 submission to the same NDA (original NDA). We provide the following comments and information requests which will serve as the basis of our teleconference scheduled for November 10, 2011.

- 1. According to your proposed label in the October 7, 2011 NDA resubmission, section 6.1, the total number of subjects administered florbetapir in clinical trials totaled “N=496 patients” (520 administrations). We note that this is the same number of subjects and florbetapir administrations stated in section 6.1 of the label submitted on September 17, 2010 in your original NDA. Based on Module 2.7.4 of Amendment 018, we are aware of at least 3 subjects who were administered florbetapir between the date of your original NDA submission (September 17, 2010) and your NDA resubmission (October 7, 2011).**
  - a. Clarify the total number of the subjects administered florbetapir between September 17, 2010 and October 7, 2011. As described in our letter of March 17, 2011, updated exposure information is important to the safety assessment for your drug. If more than 496 subjects have been exposed to your drug, you will need to revise your safety information submission, as outlined below.**
  - b. Modify section 6.1 of the draft label to account for the adverse reactions experienced by all subjects administered florbetapir prior to the date of your NDA resubmission (October 7, 2011). If there are other sections of the label that require revision based on the subjects administered florbetapir between September 17, 2010 and October 7, 2011, please update these sections before providing the updated draft label to FDA. Supply the revised safety sections of your submission to support your altered labeling.**
  - c. Provide an updated Integrated Summary of Safety (Module 5.3.5.3 in accordance with 21 CFR 314.50(d)(5)(vi)) and Summary of Clinical Safety (Module 2.7.4 in**

**accordance with 21 CFR 314.50(c)(2)(viii) which accounts for all subjects administered florbetapir before October 7, 2011 (or the data cut-off period you have chosen for your submission). In general, the data cut-off period should, at a minimum, encompass the period of time during which any subjects experienced serious adverse events or other outcomes that you regard as important to the safety assessment for your drug.**

- 2. Provide a brief description of the responsibilities of the Clinical Research Organization (CRO) in study <sup>18</sup>F-AV-45-PT01 (PT01), particularly as it applies to the process-flow of data from the readers to the primary endpoint dataset. Clarify if the source documents for study PT01 (documents that contain the reader-entered data) reside with the CRO, with Avid Radiopharmaceuticals, or with some other entity.**
- 3. Submit or provide the location of the sample histopathology electronic Case Report Form (CRF) for the PT01 study. We note that you have supplied the sample case report form for the imaging aspect (section 16.1.2 of the clinical study report). However, we need to see the CRF the pathologists completed in order to help verify the data integrity.**
- 4. Submit or identify the location of the raw (source) datasets (xpt files) for the PT01, <sup>18</sup>F-AV-45-A16 (A16), <sup>18</sup>F-AV-45-A09 (A09), and <sup>18</sup>F-AV-45-A08 (A08) studies, including the define.pdf. Submit or identify the location of the analysis datasets (xpt files) for the A16, A09, and A08 studies.**
- 5. Submit or identify the location of the results for subgroup analyses (e.g., analyses by gender, age, racial and others) for study PT01.**
- 6. Submit or identify the location of the safety data (xpt files with define.pdf) with any updated information after the original submission (as mentioned above).**
- 7. Within the electronic Case Report Tabulation (CRT) designated as Study AV45PT01 - ADSL (Module 5.3.5.3.25.3.1):**
  - a. Please clarify the development of the outcome variable, “HIGHNEUR”—which we understand to represent the highest neuritic plaque count for a subject’s brain and apparently the main determiner of amyloid positivity/negativity. Describe how this number is developed for each subject and how the number differs from the “total plaque burden” (page 19 of 45/Neuropathology Analysis Protocol) and the “average regional plaque level” cited in the <sup>18</sup>F-AV-45-A07 (A07) study report. Does the highest neuritic plaque count include both diffuse and neuritic plaques? Cite the appropriate documents that describe the composition of the amyloid plaque score that forms the standard of truth.**
  - b. Within the outcome variable of “IHC”, are the reported numbers in “% of brain”?**

We request a response as soon as possible (preferably no later than seven calendar days). If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D., Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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/s/  
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RAFEL D RIEVES  
11/07/2011



IND 79,511

**ADVICE/INFORMATION REQUEST**

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Florbetapir F 18.

We also refer you to your September 6, 2011 submission (Serial Number 129) to IND 79511 which consists of protocol changes to "Impact of Florbetapir F18 PET on the Clinical Diagnosis and Management of Patients with Progressive Cognitive Decline."

We have reviewed your submission and have the following comments and information requests:

1. We question the utility of this study in the overall drug development program for florbetapir. We are perplexed by your proposal to conduct this study based on the uncertainty in the clinical meaningfulness of a positive and negative florbetapir PET scan. Furthermore, we are concerned that the intent of this study may be to produce promotional material that we would consider inappropriate. The basis of our concern is that in the currently held expert opinion as expressed at the January 20, 2011 Advisory Committee meeting, only a negative florbetapir PET scan result would likely have any clinical meaningfulness. Yet the study is designed such that a change in clinical diagnosis in either direction based on a florbetapir PET scan would imply clinical meaningfulness, and this is not necessarily true. Describe how this study facilitates product development for florbetapir.
2. We question the necessity of the "Follow up clinic visit" given that florbetapir is still an investigational agent which has not been approved for marketing. We are concerned about the potential for harm to patients if clinical management is made based on the use of the investigational agent, florbetapir. We recommend that this follow up clinic visit be deleted from the protocol if this study is performed at all.
3. Provide your timeline for implementing this study.

IND 79,511

Page 2

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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SHARON P THOMAS  
10/06/2011



IND 79,511

ADVICE/INFORMATION REQUEST

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir F 18) Injection.

We also refer you to the minutes of the June 14, 2011 teleconference between FDA and Avid Radiopharmaceutical finalized on June 21, 2011, your August 8, 2011 submission to IND 79511 (received August 9, 2011), and your email communication on August 23, 2011. These communications pertained to the protocol and supportive information for Study 18F-AV-45-PT01. You have indicated that the image read portion of this study is ongoing. If you have not initiated any examination of the image read results and performed no analyses (i.e., all data remain blinded), you may wish to revise your analytical plans to enhance the informativeness of the data by addressing the items we outline below.

We have reviewed your August 8, 2011 submission and, if you decide to revise your protocol and its analytical plans, we have the following recommendations. We also request clarification on one topic (item 3 (b), below):

1. **Primary endpoints:** According to the June 14, 2011 teleconference minutes, FDA requested that the protocol be revised to propose and justify *primary* success criteria for inter-reader agreement and validity (performance characteristics such as sensitivity and specificity). We note that in your revised protocol, performance characteristics of image reads compared to histopathology are secondary objectives. While we do not object to this plan, we consider it an important part, nevertheless. Performance characteristics such as sensitivity and specificity are essential to assign meaningfulness to a successful primary endpoint (agreement).
2. **Success criteria for validity:** Please revise your protocol to clearly state that at least the *same* 3 out of 5 readers should achieve success on both sensitivity and specificity in order to win on the validity endpoint. Since high levels of agreement among readers do not, in themselves, ensure good diagnostic performance, FDA expects that at least 3 of the 5 readers (the same 3 of 5) achieve lower limits of confidence intervals for both sensitivity and specificity values above a pre-specified level. According to the June 14, 2011 teleconference minutes, FDA explained that the success criteria for validity should pre-

specify that the *same* 3 out of 5 readers should achieve success on both sensitivity and specificity. Based on your description of the secondary analysis on page 4 of 32 of your protocol (version August 2, 2011) and Table 13 on page 22 of 32, it is unclear to us whether your proposed success criteria is that the *same* 3 out of 5 readers achieve the  $\geq 0.50$  thresholds for the lower bounds of the 95% confidence interval for both sensitivity and specificity.

3. **Sample size:**

- a) According to the June 14, 2011 teleconference minutes, FDA requested that Avid justify the number of randomly selected images from each of the three sub-groups in A05 (AD, MCI, and HC). Your submission provided inadequate justification for including only 20 MCI subjects. Our review of your submission, in particular section 1.6 starting on page 11 of 22, raised the concern that the confidence interval may be quite wide for sample sizes less than 60 (e.g. 20 for MCI). Given that target population for your drug may largely be comprised of patients with MCI, we recommend that you increase the number of MCI subjects included in your protocol to 60. We also recommend that a large portion of the images included for intra-reader variability assessment be from MCI patients.
- b) In the cover letter you state, "...A07 protocol-defined criterion of having deceased within one year of the florbetapir-PET scan (n=46)." Our understanding is that A07 included 37 deceased subjects, with 35 undergoing autopsy. Clarify the origin of the "n=46."

4. **Type I error rate:** Clarify whether the type I error rate described on pages 4, 9, 13, 14, and 15 of 32 refers to *two-sided* type I error. We recommend that you revise the protocol to clarify this issue.

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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SHARON P THOMAS  
08/29/2011



IND 79,511

**ADVICE/INFORMATION REQUEST**

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Florbetapir F 18.

We also refer you to your submission dated April 27, 2011. We have the following comments and information requests:

1. Please revise your protocol to propose and justify primary success criteria for inter reader agreement (overall sample) and validity (performance characteristics such as both sensitivity and specificity on the autopsy sample). With respect to reader agreement, we suggest that you propose some form of multi-reader Kappa, such as can be found or referenced in standard sources such as Chapter 6 of the text "Measures of Interobserver Agreement and Reliability; Shoukri, 2<sup>nd</sup> ed". We also recommend that you modify your protocol to include adequate numbers of subjects from all three groups in your A05 study (HC, AD, MCI).
2. We recommend that you modify your reading methodology to incorporate re-reads sufficient to estimate intra reader agreement.
3. We encourage you to propose a reader confidence measure in order to assess the level of difficulty associated with interpreting images from subjects with different cognitive status. Specifically modify your case report forms to capture features of images that reflect difficulty in interpretations (such as cortical thickness). We wish to gain understanding of the image features which complicate image interpretation.
4. Regarding your reader training program:
  - a. Module 1 appears to contain unacceptable promotional information. Please be aware that these aspects will need alteration prior to clinical implementation;
  - b. Module 2 contains information particularly important to image interpretation. We encourage you to identify the most critical features of image interpretation and plan to describe these features in your product label.

IND 79,511  
Page 2

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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SHARON P THOMAS  
06/10/2011



IND 79,511

ADVICE/INFORMATION REQUEST

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Florbetapir F 18.

We also refer to your April 27, 2011 (sn 120) submission, containing your Clinical Information Amendment. We have the following Clinical Information Request:

- **Please submit your DVD or Web-based reader training program materials that will be used to educate imaging physicians.**

Please forward the materials by FedEx (by Monday, May 16, 2011) to the following address:

Sharon Thomas  
Regulatory Project Manager  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Bldg. 22, Room 5231  
Silver Spring, MD 20993

If you have any questions, please don't hesitate to contact me.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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SHARON P THOMAS  
05/11/2011

## **TELECON INTERNAL MINUTES**

**TELECON DATE:** 3/24/11 **TIME:** 12:15PM-12:45PM **LOCATION:** Conf Room1421

**NDA:** 202-008 **DRUG:** Amyvid™ (florbetapir F 18) Injection

**SPONSOR/APPLICANT:** Avid Radiopharmaceuticals

**TYPE of TELECON:** Follow-up Meeting -Post-Complete Response Action: Clarifying Deficiencies and Expected Responses.

**FDA PARTICIPANTS:**

Charley Ganley, MD, Director, ODE IV (*Meeting Chair*)  
Louis Marzella, MD, PhD -Acting, Division Director, DMIP  
Lucie Yang, MD, PhD- Acting, Team Leader (TL), DMIP  
Qi Feng, MD, PhD- Primary Clinical Reviewer, DMIP  
Sharon Thomas, Regulatory Project Manager, DMIP (*Meeting Recorder*)

**INDUSTRY PARTICIPANTS:**

Dan Skovronsky, MD, PhD – CEO  
Alan Carpenter, PhD, JD – Vice President, Legal & Regulatory Affairs  
Mark Mintun, MD – Chief Medical Officer  
Mike Krautkramer – Senior Director, Project Management  
Christine Gathers, Sr. Director, Global Regulatory Affairs, Diagnostics, Eli Lilly

**BACKGROUND:**

The FDA requested a follow- up teleconference to discuss Avid’s “In-person” training program. Avid agreed to the teleconference on March 23, 2011. The discussion points are indicated in *bold italics* below.

*FDA asked Avid about its “in-person” training program, specifically the need to have someone to be able to provide real-time feedback on how to read the scans. Avid acknowledged that multiple training methods would be useful, but felt that the “in-person” training method would be the most feasible to develop and validate first. FDA needed more information on how this program could be implemented. Once the drug was approved, there would be a demand for training. It was not clear how Avid would be able to accommodate all of the requests. It is also not clear how this would be implemented with regulatory oversight. FDA requested more details so that we could discuss the program*

*internally to determine whether this is something that is feasible from a regulatory point of view.*

*FDA encouraged Avid to develop a training program that could be universally applied and easily accessible. FDA proposed a training manual that could be downloaded from a website which would provide reader accuracy and consistency. FDA suggested that they pilot something such as this as they moved forward with the in-house training.*

*FDA asked for feedback on how the Agency could implement Avid's "in-person" training plan into labeling. FDA stated that the "in-person" training program would be complicated from a regulatory standpoint and may have to be enforced through a REMS.*

*Avid acknowledged that they were aware of the letter from Public Citizen that expressed concerns about the ability of readers to interpret the images for Amyvid.*

*FDA expressed concern with the "in-house" training method used in the A08 and A09 studies, but acknowledged that the data appeared promising. FDA encouraged Avid to convert the A08 and A09 data into a training manual and use it to test a reader's performance.*

*Avid agreed to re-visit their "in-person" training method, develop a training manual and/or pilot program with an evaluation plan. FDA proposed to discuss the A08 and A09 data with the statisticians to define the success criteria on the number of readers needed.*

*FDA asked Avid to submit a summary of their "in-person" training program and how it would be implemented for review and feedback. Avid concurred.*

#### **UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no unresolved issues.

#### **ACTION ITEMS:**

- Avid to submit a outline of their proposal for their "in-person" training program within the next week.
- FDA will have further internal discussions with our statisticians to determine the number of readers necessary to validate the training program.

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/s/  
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SHARON P THOMAS  
03/31/2011

## **TELECON INTERNAL MINUTES**

**TELECON DATE:** 3/22/11 TIME: 1:30PM-2:00PM

**LOCATION:** CDER WO Conf Room1417

**NDA:** 202-008

**DRUG:** Amyvid™ (florbetapir F 18) Injection

**SPONSOR/APPLICANT:** Avid Radiopharmaceuticals

**TYPE of TELECON:** Post-Complete Response Action: Clarifying Deficiencies and Expected Responses.

### **FDA PARTICIPANTS:**

Louis Marzella, MD, PhD -Acting, Division Director, DMIP  
Shaw Chen, MD, PhD- Deputy Div. Director, ODE IV  
Lucie Yang, MD, PhD- Acting, Team Leader (TL), DMIP  
Qi Feng, MD, PhD- Primary Clinical Reviewer, DMIP  
Ira Krefting, MD- Safety Clinical Reviewer, DMIP  
Brenda Ye, MD- Medical Officer, DMIP  
Scheldon Kress, MD, Medical Officer, DMIP  
Diem-Kieu Ngo, (CDR,USPHS), Advisory Committee Rep.  
Sunday Awe, PhD, MBA Pharm/Tox. Reviewer, DMIP  
Ravindra Kasliwal, PhD, CMC Reviewer, ONDQA  
Eldon Leutzinger, PhD, CMC TL, ONDQA  
Frank Perrella, PhD, Compliance Officer  
Peter Diak, PharmD, MPH , Safety Evaluator TL, OSE  
Michael Kieffer, PharmD, MPH, Safety Evaluator, OSE  
Sandra Griffith, RN, BSN, Safety Project Manager, OSE  
Adora Ndu, PharmD, DDMAC Reviewer

### **INDUSTRY PARTICIPANTS:**

Dan Skovronsky, MD, PhD – CEO  
Alan Carpenter, PhD, JD – Vice President, Legal & Regulatory Affairs  
Mark Mintun, MD – Chief Medical Officer  
Mike Pontecorvo, PhD – Vice President, Clinical Development  
Mike Krautkramer – Senior Director, Project Management  
Christopher Clark, MD, Medical Director  
Franz Heft, PhD, Chief Scientific Officer

John Lister-James, PhD, VP, Chemical Development and Manufacturing  
Christine Gathers, Sr. Director, Global Regulatory Affairs, Diagnostics, Eli Lilly

## **BACKGROUND:**

At the conclusion of FDA's review of NDA 202-008, as designated by the issuance of a complete response letter on March 17, 2011, FDA provided the applicant with an opportunity to meet with agency reviewing officials. On March 17, 2011, the sponsor agreed to a teleconference to obtain clarification, specifically for the implementation of items outlined in the complete response letter and the next steps to be taken before the application could be approved. They also submitted 6 questions to facilitate the discussion. The discussion points are indicated in ***bold italics*** below.

## **QUESTIONS for DISCUSSION and DECISIONS REACHED:**

### Question 1:

Materials of training – Avid proposes that the training materials will comprise the following: slides, script, FAQs, recommended report template, and training / testing case studies (per FDA recommendations). We intend to submit these materials to FDA for review; are these the materials that FDA is requesting (point 3 of CRL)? What is the FDA process for review and feedback?

#### **Discussion Point:**

***Avid inquired about the FDA's process for review of the above training materials. Avid noted that the training materials may become apart of labeling and future marketing materials.***

***FDA asked for clarification on Avid's plan to train new readers. FDA recommended electronic media or website training because it seemed more feasible. Avid stated that they are considering a variety of training methods but the first training method they plan to implement comprises of an "in-person" training session rather than a website or electronic media. In response, FDA stressed that the qualifications of the individuals employed as a trainer should be submitted along with the training materials. Avid stated that before readers are trained using a website or compact disc (CD), they will also validate these materials and submit such validation to FDA for review.***

***FDA discussed the review process for feedback. FDA advised Avid to submit a Type C meeting request or an amendment with questions. FDA will do its best to provide comments within 90 days of receiving the amendment submission.***

### Question 2:

Methods of training – Avid proposes to train with the above training materials in the following manner: In-person training sessions (either regional or on-site) by qualified trainer. Would this be sufficient/appropriate for the NDA?

**Discussion Point:**

***This question was discussed together with question 1.***

Question 3:

Validation of training – Avid believes the Agency is asking us to validate the above training method (utilizing the above training materials) in the setting of the physician offices / radiology reading rooms (using a predefined protocol). Does the Agency consider this to be a “clinically applicable” setting?

**Discussion Point:**

***Avid inquired about the clinically appropriate setting for validation of the training methods. FDA concurred with Avid’s proposed settings, i.e. physician offices and imaging labs. FDA requested that Avid incorporate processes within the protocol to ensure blinding, lack of bias, verifiability of processes. Avid asked about specific suggestions since readers would be on their own in their offices. FDA suggested that trainers should not have any idea about the subject’s age or birthdate and that images be randomized.***

Question 4:

Protocol/design of training validation – Avid will submit a protocol, as requested, prior to validation of training, with the proposed number of subjects and number of readers which are appropriate to achieve certain predefined statistical endpoints. Avid anticipates FDA feedback on the protocol design. It is not clear that all 336 cases should be read as part of the validation protocol. With appropriate statistical justification is it acceptable to read a randomly selected subset of the cases in A07 and A05 for validation? (However, all autopsied patients would be included.) Is this consistent with the FDA expectation? Avid proposes to adopt the previous FDA success criteria for reader sensitivity and specificity (from FDA AC Briefing Document). Is this still appropriate?

**Discussion Point:**

***Avid noted that all of A07 and A05 subjects would add up to 336 cases and proposed a randomly selected subset. FDA explained that the statistical reviewers were not present and requested that Avid submit statistical justification for review. FDA also commented that each reader should interpret images over several sessions rather than read the entire set of images on the same day following training earlier that day.***

Question 5:

Pathology reference standard -- Avid has proposed/is proposing to define [REDACTED] (b) (4), and will provide information in the PI to clarify

(b) (4) in various clinical presentations using current guidelines. Is this appropriate?

**Discussion Point:**

***FDA did not object to Avid's proposal.***

Question 6:

Avid intends to work with PETNET and Cardinal to address the manufacturing site 483 observations. Following submission of the responses, what will be the FDA process for resolution? How does Avid know that we have adequately addressed these observations? Does the Agency agree that we do not need to address the FDG-specific concerns prior to approval?

**Discussion Point:**

***FDA noted that the Agency may re-inspect the facility to confirm that the 483 observations have been corrected. If inspected, the narrative portion of the EIR should be released to the establishment inspected. The firm should wait for action from the Review Division. All observations on the 483 should be addressed prior to approval, regardless of whether the deficiencies relate to florbetapir. The sponsor was encouraged to begin addressing the 483 observations now rather than wait until submission of materials to address the Complete Response.***

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no unresolved issues.

**ACTION ITEMS:**

Avid to submit a Type C meeting request or an amendment with questions.

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/s/  
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SHARON P THOMAS  
03/31/2011

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Thursday, March 17, 2011 5:05 PM  
**To:** 'Alan Carpenter'  
**Subject:** Amyvid NDA 202-008  
**Attachments:** FINALAmyvidComplete Response3-17-11CLEAN.pdf

Dear Dr. Carpenter,

Please find attached the Complete Response (CR) letter for your NDA 202-008, submitted on September 17, 2010 for Amyvid™ (Florbetapir F 18 Injection).

As indicated on page #9, under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants."

Please confirm receipt of this email. Should you have any questions, please don't hesitate to contact me.

Sincerely

*Sharon*

Sharon Thomas, RPM  
Division of Medical Imaging Products  
Office of Drug Evaluation IV, CDER, FDA  
Phone: (301) 796-1994  
Fax: (301) 796-9849  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

3/23/2012

**From:** Thomas, Sharon  
**Sent:** Wednesday, February 16, 2011 3:04 PM  
**To:** 'Alan Carpenter'  
**Subject:** NDA 202-008/Amyvid/ Labeling

Dear Dr. Carpenter,

We are notifying you that we are maintaining consistency with the 21<sup>st</sup> Century review procedures for your application. According to these procedures, we typically provide an update on labeling findings at this time. Please be aware that based on preliminary review findings regarding NDA 202008, we are not currently engaged in labeling review.

Sincerely,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Monday, January 24, 2011 5:48 PM  
**To:** 'Alan Carpenter'  
**Cc:** 'Michael Krautkramer'; 'Kristin White-Levine'  
**Subject:** Clinical Information Request- Please respond by 12:00 PM, Jan 25th  
**Attachments:** 202008Clinical IR 012411.pdf

Dr. Carpenter,

Please find attached a Clinical Information Request for Amyvid. Please provide comments via email by 12:00 pm, Tuesday, January 25, 2011.

Please don't hesitate to contact me if you have any questions.

Sharon Thomas, RPM

## Thomas, Sharon

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**From:** Thomas, Sharon  
**ent:** Saturday, January 15, 2011 8:07 PM  
**To:** 'Alan Carpenter'  
**Subject:** NDA 202008- CMC Information Request- Deficiencies

**Attachments:** CMCIR.pdf

Hi Dr. Carpenter,

Attached is a CMC information request for Amyvid. Please don't hesitate to contact me if you have any questions.



CMCIR.pdf (54 KB)

Thank you,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Monday, January 10, 2011 5:38 PM  
**To:** 'Alan Carpenter'  
**Cc:** 'Michael Krautkramer'; 'David Haenick'; 'Kristin White-Levine'  
**Subject:** RE: Clinical and Micro - Information Requests - NDA 202008-Amyvid  
**Attachments:** Clinical202008Information Request011011.pdf; Micro202008Information Request011011.pdf

Good afternoon Dr. Carpenter,

Attached are two Information Requests from our clinical and microbiology review teams for Amyvid.

Please don't hesitate to contact me if you have any questions.

Thank you,  
Sharon Thomas

2/15/2011

## Thomas, Sharon

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**From:** Thomas, Sharon  
**ent:** Tuesday, November 30, 2010 1:40 PM  
**fo:** 'Alan Carpenter'  
**Cc:** 'Kristin White-Levine'  
**Subject:** RE: NDA 202-008 Amyvid - Clinical Information Request

**Attachments:** 202008 ClinPharmInformation Request 112910.pdf

Dear Dr. Carpenter,

Attached is a Clinical Pharmacology Information Request for Amyvid. Please provide a response on or before, December 6, 2010.

Please don't hesitate to contact me if you have any questions.

Thank you,  
Sharon



202008

**PharmInformation R**

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
DE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax

## Thomas, Sharon

---

**From:** Thomas, Sharon  
**ent:** Wednesday, November 24, 2010 3:02 PM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** NDA 202-008 Amyvid - Clinical Information Request

**Attachments:** 202008 ClinInformation Request 112410.pdf

Dear Dr. Carpenter,

Attached is a Clinical Information Request for Amyvid. Please provide a response before or by Wed., December 1, 2010.

Is it possible for you to submit Avid's slides from yesterday's meeting via email today? If not, can you convey them on Friday and submit them formally to the NDA.

Please don't hesitate to contact me if you have any questions.

Thank you,  
Sharon



202008

Information Request

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Tuesday, November 16, 2010 6:26 PM  
**To:** 'Alan Carpenter'  
**Cc:** Michael Krautkramer; Kristin White-Levine  
**Subject:** RE: Slides and articles: Avid-FDA meeting 15-Nov-2010

Hi Dr. Carpenter,

Thank you for providing the slides from yesterday's Presentation Meeting. The Division has requested a follow-up meeting, specifically for Tuesday, November 23, 2010, 11:00 AM- 12:30 PM at our White Oak facility.

Also, please indicate if Avid plans to make any more proposals for the Amyvid labeling that describes how to interpret and report the images.

Thank you again for the slides and when you have an opportunity, please confirm the meeting date/time.

Best regards,

Sharon Thomas, RPM  
Division of Medical Imaging Products

---

**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Tuesday, November 16, 2010 6:02 PM  
**To:** Thomas, Sharon  
**Cc:** Michael Krautkramer; Kristin White-Levine  
**Subject:** Slides and articles: Avid-FDA meeting 15-Nov-2010

Ms. Thomas,

Please find attached pdf slides from yesterday's presentation by Avid. Following our meeting, upon reflection on the comments made by the Agency at our meeting, we have also prepared two additional slides on the ROC analysis, which substitute CERAD plaque score as the reference standard in place of NIA-Reagan neuropath diagnosis. Not too surprisingly, the curves are essentially identical. Nevertheless, we wanted to make sure that the review team understood that CERAD as a reference standard provides a similar result to NIA-Reagan.

I have also attached two articles which were referenced at yesterday's meeting; the Wisniewski Acta Neuropath article, which compares multiple methods of amyloid measurements, including IHC with the 4G8 antibody and Bielschowsky histopathology measurement of neuritic plaque count. The second article is the Loy 2004 JAMA article on the impact of clinical information on diagnostic test accuracy.

Avid intends to submit these same materials as an NDA amendment via the gateway within the next day, per your recommendation at the meeting yesterday.

Finally, we also intend to provide complete written responses to all questions as an NDA amendment within the next 2 weeks, unless you advise otherwise.

Please extend our thanks again for the time provided by the Division for this meeting yesterday.

2/15/2011

Sincerely,

Alan Carpenter

Alan P. Carpenter Jr., Ph.D., J.D.  
Vice President, Legal and Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th floor  
Philadelphia, PA 19104  
215-298-0707  
857-928-4520 (mobile)  
carpenter@avidrp.com

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**Sent:** Friday, November 12, 2010 11:20 AM  
**To:** 'Alan Carpenter'  
**Subject:** RE: Filing Letter- Amyvid NDA 202-008  
**Attachments:** ly\_qf\_dr\_clin\_stats\_202008No Filing Issues Identified 111010 (2).pdf

Hi Dr. Carpenter,

Please find attached an e-copy of the 74 day filing letter for Amyvid. You will also receive a hard copy next via postal delivery. Please don't hesitate to contact me if you have any questions.

Thank you,  
Sharon

---

**From:** Thomas, Sharon  
**Sent:** Thursday, November 11, 2010 8:30 PM  
**To:** 'Alan Carpenter'  
**Subject:** RE: Information Request- Amyvid NDA 202-008

Dear Dr. Carpenter,

We would like you to focus the presentation on the items below first and then continue with the presentation from the last meeting. Please note that we made minor revisions to the information requests/comments sent on 11/10/10. The items below will be included in the NDA Filing letter.

Thank you,  
Sharon

- 1. The image interpretation methodological aspects of Study A07 are not readily apparent, especially with respect to the proposed labeling and clinical use of your product.**
  - a. We are concerned that the proposed labeling may not sufficiently describe the methodology essential to image interpretation, including the strengths and limitations of image interpretation. Conceivably, a training manual or other tools may need to be incorporated into the labeling.**
  - b. We are also concerned that the data may not provide sufficient verification that the proposed labeling ensures a clinical nuclear medicine physician will interpret the images obtained with your product in a manner that reliably estimates the brain content of amyloid. We note that, among the three readers for the autopsy portion of the study, potentially important inconsistency was evident for at least one reader in a number of patients. This preliminary observation will need closer review but we are concerned that even greater inconsistency in image interpretation may occur in clinical practice, particularly in light of the proposed labeling. The relatively limited data pertaining to image interpretation reproducibility may present a special challenge.**

2/15/2011

- c. With respect to the potential clinical use of your product, the role of incorporating clinical information into image interpretation is not readily apparent. We are concerned that insufficient information is available to assess the role, if any, of incorporating clinical information into image interpretation. In practice, nuclear medicine physicians generally consider clinical information. The available data do not appear to assess the extent to which clinical information will impact the reliability of amyloid estimation with your product.
2. Several aspects of the image ascertainment and interpretation methodology were not readily apparent. Below we provide several initial requests to exemplify our need for clarification. These items relate to Study A07.

We request that you submit the following information:

3. Computed Tomographic (CT) aspect of the PET imaging protocol:
- a. What was the standard PET imaging protocol? **If this information is in the submission, please identify the location.**
- b. Did all subjects who underwent a PET scan undergo a CT scan on the same day as the PET scan? From the document “Listing 16.2.4.9 Additional Imaging Safety Population” of clinical study report of A07, we note that some subjects underwent a CT scan on the PET imaging day but others apparently did not.
- c. What is the total radiation exposure due an Amyvid PET/CT scan? We understand that 10 mCi Amyvid results in 7.03 mSv. Provide the radiation exposure due to the CT scan.

4. Independent Review Training Manuals:

Comment on the rationale for having two different independent review training manuals for training the PET image readers (autopsy versus the “specificity” cohort). Specifically, comment on the rationale for the different rating scales (semi-quantitative 5-point scale from 0-4 versus positive / negative versus semi-quantitative 3-point scale from 0-2).

5. Reader Training:

Section 6.3 of document 2.7.3 Summary of Clinical Efficacy summarizes the training of PET image readers.

- a. Is the cited Independent Review Training Manual the same as those manuals cited in section 5.3.5.1.4 Protocol or Amendment? We suggest you develop a cohesive and detailed description of the reader training procedures (as they were planned and as they were conducted).
- b. Submit the PowerPoint presentation that is referred to in this section. If this is already in the submission, please identify the location.

6. **PET image reader:**

One PET reader had previous experience reading PET images for the presence of amyloid. Was this PET reader with previous experience Reader 1, 2, or 3 in Table 11-10 on page 70 of document 5.3.5.1.3 Study AV45A07 – Study Report Body?

7. **Reading session:**

During a reading session of PET images for the autopsy cohort,

- a. Clarify the types of interpretation and the order of the interpretations a reader was to perform for an individual subject. In other words, was the reader to make a global rating on the semi-quantitative scale, then a rating for each of 6 regions on the semi-quantitative scale, and then draw regions of interest for the SUV determination in various regions, etc? Discuss the compliance with the planned procedures.
- b. Clarify the timing of the data locks relative to each interpretation for each reader. In other words, was a rating (such as the semi-quantitative global rating) locked before a reader proceeded to the next rating (such as semi-quantitative regional rating) or did the data lock occur only after a reader finished all evaluations and ratings for a given subject?
- c. Clarify whether readers of PET images had access to images both in color and in black-and-white. Thoroughly describe the image display and manipulation options.
- d. Confirm that the PET readers had access to any anatomic images (such as CT) during the reading of PET images.
- e. If the above information is already in the submission, please identify the location.
- f. Clarify the above items regarding the reading session of PET images for the specificity cohort. If this information is already in the submission, please identify the location.

8. **Autopsy cohort images randomized into specificity cohort images:**

- a. PET images from 40 autopsy cohort subjects were randomized into the specificity cohort images to reduce bias. The autopsy cohort images that were added to the specificity cohort images had a median read of 2, 3, or 4 by the three readers for the **autopsy cohort**. **Comment on your rationale to not also add images from autopsy cohort subjects who had <1% area occupied by amyloid by immunohistochemistry.**
- b. For the 40 subjects from the autopsy cohort whose PET images were randomized into the images of the specificity cohort for PET image readers,
  - i. provide the subject number and ages of these subjects in ascending order in tabular format. If this information is in the submission, please identify the location.
  - ii. provide details regarding any additional criteria used to choose the images (if there were criteria other than a median rating of 2, 3, or 4 by readers of the

autopsy cohort).

- c. For the subjects in the autopsy cohort whose images were not chosen to be randomized into the images of the specificity cohort for PET image readers,
- i. provide the ages of these subjects in ascending order in tabular format. In this same table, include the subject number, the percent area occupied by amyloid on immunohistochemistry for those who underwent autopsy, the median rating by readers of images from the autopsy cohort, and the rating by the three individual readers.

9. SUVR:

- a. Comment on the reliability of SUVR as a quantitative parameter in the imaging assessment and the threshold of 1.1 you use for some exploratory analyses. We note that the SUVR of 3 negative autopsy subjects with IHC less than 1%, actually less than 0.05%, in A07 trial can be easily rounded up to 1.1.

Subject	IHC (%)	SUVR
054-002	0.001	1.086
059-003	0.011	1.069
062-001	0.042	1.091

- b. Comment on the reliability of the SUVR measurement in light of the many factors that can influence SUVR. We note that the SUVR of subjects with a wide range of IHC % area amyloid can apparently have very similar SUVR.

Subject	IHC (%)	SUVR
522-001	1.105	1.639
137-005	9.442	1.569

10. Silver Staining:

Clarify the process for determining the final histopathological result based on silver staining which was used in exploratory analyses in Study A07. On the file named "Bielschowsky silver stain plaque counts from readers and neurologist overread" you submitted in response to our information request issued 20 October 2010, we observe what appear to be inconsistencies in the determination of plaque counts based on reader 1, reader 2, and NP overread. Clarify the basis for the "NP overread" generating a number which is different from both readers 1 and 2.

11. Immunohistochemistry:

- a. Section 7.3.2 of document 5.3.5.1.4 Study AV45A07 – Protocol (version 12 November 2009) states that the global assessment of amyloid burden is based on the average results from six target brain areas (superior-middle temporal gyrus, middle frontal

**gyrus, inferior parietal lobule, anterior cingulate gyrus, precuneus, posterior cingulate gyrus).** Comment on the criteria used to choose these six brain regions.

- b. Comment on whether immunohistochemistry for A $\beta$  is used clinically. If so, for what purpose? Also, comment on whether any threshold(s) for percent area occupied by amyloid is used in clinical practice. If so, comment on the clinical implication(s) of such thresholds.

12. **Data in the NDA:**

Regarding subjects 18F-AV-45-A07-152-001 (SUVR 0.91754) and 18F-AV-45-A07-145-001 (SUVR 1.38165), we are unable to find SUV data in the document "Listing 16.2.10.6 Flortetapir-PET Brain Imaging Results: Standard Uptake Values (SUVs)". We found the SUVRs of these two subjects. Please advise regarding the location of the original SUV data in the submission. Also, clarify how SUVR was calculated.

13. **Test validity:**

Comment on the validity of the Amyvid PET scan, particularly with respect to the use of SUV measurements in the image interpretation process. We note good correlation between IHC and autoradiography of human brain tissue *in vitro* ( $\rho = 0.889$  and  $p < 0.001$ ), but the correlation of cortical IHC and cortical SUV does not appear as robust.

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**From:** Alan Carpenter [mailto:carpenter@avidrp.com]  
**Sent:** Thursday, November 11, 2010 8:48 AM  
**To:** Thomas, Sharon  
**Subject:** RE: Information Request- Amyvid NDA 202-008

Dear Ms. Thomas,

Thank you for the additional questions for discussion at the meeting on Monday.

Attendees from Avid will be:

Daniel Skovronsky, CEO  
 Mark Mintun, Chief Medical Officer  
 Michael Pontecorvo, Vice President, Clinical Development  
 Michael Krautkramer, Director, Project Management  
 Franz Hefti, Chief Scientific Officer  
 John Lister-James, Vice President, Chemical Development & Manufacturing

(b) (4)

(b) (4)

(b) (6) The form for Dr Lister-James is attached.

Please let me know which Bldg and room we are meeting in. We will arrive at the lobby by 11:45am.

Can you please advise me whether we should continue the presentation of the slides from the last meeting (Oct

2/15/2011

7) or focus the presentation on these recent questions?

Thank you.

Alan Carpenter

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Alan P. Carpenter, Jr., Ph.D., J.D.  
Vice President, Legal & Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104  
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[carpenter@avidrp.com](mailto:carpenter@avidrp.com)

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**From:** Thomas, Sharon [mailto:Sharon.Thomas@fda.hhs.gov]  
**Sent:** Wednesday, November 10, 2010 5:57 PM  
**To:** Alan Carpenter  
**Subject:** Information Request- Amyvid NDA 202-008

Dear Dr. Carpenter,

Please find below the items we would like you to address in the sponsor presentation meeting scheduled on Monday, Nov., 15th. Also, please provide Avid's list of attendees to clear security.

Thank you,  
Sharon Thomas, RPM

---

1. CT aspect of the PET imaging protocol

2/15/2011

- a. What is the standard PET imaging protocol? If this information is in the submission, please instruct regarding the location.

**Did all subjects who underwent a PET scan undergo a CT scan on the same day as the PET scan?**

From the document "Listing 16.2.4.9 Additional Imaging Safety Population" of clinical study report of A07, we note that some subjects underwent a CT scan on the PET imaging day but others did not.

**What is the total radiation exposure due an Amyvid PET/CT scan? We understand that 10 mCi Amyvid results in 7.03 mSv. Provide the radiation exposure due to the CT scan.**

Independent Review Training Manuals

Comment on the rationale for having two different independent review training manuals for training the PET image readers. Specifically, comment on the rationale for the different rating scales (semi-quantitative 5-point scale from 0-4 versus positive / negative versus semi-quantitative 3-point scale from 0-2).

Reader Training

Section 6.3 of document 2.7.3 Summary of Clinical Efficacy summarizes the training of PET image readers.

- a. Is the Independent Review Training Manual that is referred to the same as those in section 5.3.5.1.4 Protocol or Amendment?

**Submit the PowerPoint presentation that is referred to in this section. If this is already in the submission, please instruct regarding the location.**

PET image reader

One PET reader had previous experience reading PET images for the presence of amyloid. Was this PET reader with previous experience Reader 1, 2, or 3 in Table 11-10 on page 70 of document 5.3.5.1.3 Study AV45A07 – Study Report Body?

Reading session

During a reading session of PET images for the autopsy cohort,

- a. Clarify the types of interpretation and the order of the interpretations a reader does for an individual subject. In other words, does the reader make a global rating on the semi-quantitative scale, then a rating for each of 6 regions on the semi-quantitative scale, and then draw regions of interest for the SUV determination in various regions, etc?

**Clarify the timing of the data locks relative to each interpretation for each reader. In other words, was a rating (such as the semi-quantitative global rating) locked before a reader proceeded to the next rating (such as semi-quantitative regional rating) or did the data lock occur only after a reader finished all evaluations and ratings for a given subject?**

**Clarify whether readers of PET images had access to images both in color and in black-and-white.**

Confirm that the PET readers had access to any anatomic images such as CT during the reading of PET images.

If the above information is already in the submission, please instruct regarding the location.

Clarify the above items regarding the reading session of PET images for the specificity cohort. If this information is already in the submission, please instruct regarding the location.

Autopsy cohort images randomized into specificity cohort images

- a. PET images from 40 autopsy cohort subjects were randomized into the specificity cohort images to reduce bias. The autopsy cohort images that were added to the specificity cohort images had a median read of 2, 3, or 4 by the three readers for the autopsy cohort. Comment on your rationale to not also add images from autopsy cohort subjects who had <1% area occupied by amyloid by immunohistochemistry.

**For the 40 subjects from the autopsy cohort whose PET images were randomized into the images of the specificity cohort for PET image readers,**

- i. provide the subject number and ages of these subjects in ascending order in tabular format. If this information is in the submission, please advise regarding the location.

**provide details regarding any additional criteria used to choose the images (if there were criteria other than a median rating of 2, 3, or 4 by readers of the autopsy cohort).**

**For the subjects in the autopsy cohort whose images were not chosen to be randomized into the images of the specificity cohort for PET image readers,**

- i. provide the ages of these subjects in ascending order in tabular format. In this same table, include the subject number, the percent area occupied by amyloid on immunohistochemistry for those who underwent autopsy, the median rating by readers of images from the autopsy cohort, and the rating by the three individual readers.

SUVR

- a. Comment on the reliability of SUVR as a quantitative parameter in the imaging assessment and the threshold of 1.1 you use for some exploratory analyses. We note that the SUVR of 3 negative autopsy subjects with IHC less than 1%, actually less than 0.05%, in A07 trial can be easily rounded up to 1.1.

Subject	IHC (%)	SUVR
054-002	0.001	1.086
059-003	0.011	1.069
062-001	0.042	1.091

**Comment on the reliability of the SUVR measurement in light of the many factors that can influence SUVR. We note that the SUVR of subjects with a wide range of IHC % area amyloid can have very similar SUVR.**

Subject	IHC (%)	SUVR
522-001	1.105	1.639
137-005	9.442	1.569

### Silver Staining

Clarify the process for determining the final histopathological result based on silver staining which was used in exploratory analyses in Study A07. On the file named "Bielschowsky silver stain plaque counts from readers and neurologist overread" you submitted in response to our information request issued 20 October 2010, we observe what appear to be inconsistencies in the determination of plaque counts based on reader 1, reader 2, and NP overread. Clarify the basis for the "NP overread" generating a number which is different from both readers 1 and 2.

### Immunohistochemistry

- a. Section 7.3.2 of document 5.3.5.1.4 Study AV45A07 – Protocol (version 12 November 2009) states that the global assessment of amyloid burden is based on the average results from six target brain areas (superior-middle temporal gyrus, middle frontal gyrus, inferior parietal lobule, anterior cingulate gyrus, precuneus, posterior cingulate gyrus). Comment on the criteria used to choose these six brain regions.

**Comment on whether immunohistochemistry for A $\beta$**  is used clinically. If so, for what purpose? Also, comment on whether any threshold(s) for percent area occupied by amyloid is used in clinical practice. If so, comment on the clinical implication(s) of such thresholds.

### Data in the NDA

Regarding subjects 18F-AV-45-A07-152-001 (0.91754) and 18F-AV-45-A07-145-001 (1.38165), we are unable to find SUV data in the document "Listing 16.2.10.6 Florbetapir-PET Brain Imaging Results: Standard Uptake Values (SUVs)". We found the SUVRs of these two subjects. Please advise regarding the location of the original SUV data in the submission. Also, clarify how SUVR was calculated.

### Test validity

Comment on the validity of the Amyvid PET scan. We note good correlation between IHC and autoradiography of human brain tissue *in vitro* ( $\rho = 0.889$  and  $p < 0.001$ ), but the correlation of cortical IHC and cortical SUV does not appear as robust.

(Please note that we will include the comments above in the NDA filing letter.)

**Thomas, Sharon**

---

**From:** Thomas, Sharon  
**ent:** Wednesday, November 03, 2010 9:18 PM  
**To:** 'Alan Carpenter'  
**Subject:** NDA 202008- Amyvid (florbetapir F 18) Injection- CMC Information Request  
**Attachments:** CMC202008Information Request110310.pdf

Dear Dr. Carpenter,

Please find enclosed a CMC information request for Amyvid (florbetapir F 18) Injection. Please provide a response by November 8, 2010.

Sincerely,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax



**CMC202008Informa**  
tion Request11...

## Thomas, Sharon

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**From:** Thomas, Sharon  
**ent:** Wednesday, October 20, 2010 5:21 PM  
**To:** 'Alan Carpenter'  
**Subject:** Clinical /Statistical Information Request- NDA 202-008 Amyvid, florbetapir  
**Attachments:** 202008 ClinInformation Request 102010.pdf

Hi Dr. Carpenter,

Please find attached a clinical/statistical information request for NDA 202-008, for florbetapir. Please provide a response before COB on Monday, 10/25/10.

Thank you,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax



202008

Information Request

## Thomas, Sharon

---

**From:** Thomas, Sharon  
**ent:** Thursday, October 14, 2010 4:13 PM  
**To:** 'Alan Carpenter'  
**Subject:** Advisory Meeting- NDA 202-008

Hi Dr. Carpenter,

On January 21, 2011, the Agency will discuss your new drug application (NDA) submitted for florbetapir at an Advisory Committee Meeting. A representative from our Advisory Group will contact you and provide further details and logistics. Please don't hesitate to contact me if you have any questions.

Best regards,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax

## Thomas, Sharon

---

**From:** Thomas, Sharon  
**ent:** Tuesday, October 12, 2010 11:47 AM  
**To:** 'Alan Carpenter'  
**Cc:** Kristin White-Levine  
**Subject:** IND 79,511

**Attachments:** PharmTox 79511Advice-Information Request10-12.pdf

Dear Dr. Carpenter,

Please find attached the Advice letter regarding your request for a waiver of carcinogenicity studies.

Please don't hesitate to contact me if you have any further questions.

Thanks,

*Sharon Thomas*

Regulatory Project Manager  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA

(301)796-1994 phone  
(301) 796-9849 fax



PharmTox  
11Advice-Infomat

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**ent:** Wednesday, September 22, 2010 10:46 AM  
**To:** 'Alan Carpenter'  
**Subject:** FW: Inspections- NDA 202-008

Hi Dr. Carpenter,

Per our discussion, please see the following information from the clinical reviewer:

We understand that in your 18F-AV-45-A07 study, there were 34 study centers in the United States, 25 of which enrolled at least 1 subject.

1. Any site out of USA?
2. Is there a summary table of site #, address, PI name and subject # of A-07 and all other studies in the submission? If yes, please specify the location.
3. Is there any summary of conflict of interest (COI) of the PIs (PI receiving grant from the sponsor, Avid)? Are there individual statements of the all the PIs on the issue in the submission? If yes, please specify the location.

Thanks,  
Sharon

## Thomas, Sharon

---

**From:** Thomas, Sharon  
**ent:** Monday, August 09, 2010 3:56 PM  
**fo:** 'Alan Carpenter'  
**Subject:** RE:Quality- FDA Responses- IND 79511  
**Attachments:** CMC79511Advice-Information Request8-9.pdf

Dear Dr. Carpenter,

Please find attached our CMC/Micro. responses to your questions submitted in your briefing package dated 6/22/10. Please don't hesitate to contact me if you have any questions.

Thank you very much,

Sharon Thomas, RPM



CMC79511Advice-I  
nformation Req...

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/s/  
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SHARON P THOMAS  
02/16/2011

# DIVISION OF MEDICAL IMAGING PRODUCTS

## TELECON

**DATE:** February 2, 2011

**TIME:** 12:00 PM

**LOCATION:** 2327

**APPLICATION:** NDA 202-008

**DRUG NAME:** AMYVID (Florbetapir F 18) Injection

**SPONSOR:** Avid Radiopharmaceuticals

### FDA ATTENDEES:

Qi Feng, M.D., Primary Clinical Reviewer

Rafel Dwaine Rieves, M.D., Division Director (*Meeting Chair*)

Lucie Yang, M.D., Ph.D., Clinical Reviewer

Sharon Thomas, Regulatory Project Manager (*Meeting Recorder*)

### SPONSOR:

Alan Carpenter, JD, Regulatory Affairs, Avid

Mark Minton, MD, Clinical Reviewer, Avid

Dan Snovronsky, CEO, Avid

### SUMMARY:

The sponsor requested a teleconference to discuss the next steps for the Amyvid application. FDA responded that the team will focus reviews on the data provided in original submission of the NDA. The sponsor inquired if the FDA reviewed the Reader Training Independent Review Charter submitted on January 10, 2011. FDA expressed the challenge of sending tentative feedback and explained that if egregious problems were seen, the Agency will contact the sponsor. The sponsor discussed their plans to submit additional study reports on February 7, 2011 and inquired about a major amendment submission. FDA noted that it would be a review issue.

## **DIVISION OF MEDICAL IMAGING PRODUCTS**

### **WRAP UP MEETING**

**DATE:** January 24, 2011 **TIME:** 2:30 PM **LOCATION:** 1421

**APPLICATION:** NDA 202-008 **DRUG NAME:** AMYVID (Florbetapir F 18) Injection

**SPONSOR:** Avid Radiopharmaceuticals

#### **FDA ATTENDEES:**

Sunday Awe, Ph.D., Pharm\Tox Reviewer  
Laniyou, Adebayo, Ph.D., Pharm/Tox Team Leader  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Qi Feng, M.D., Primary Clinical Reviewer  
Alex Gorovets, M.D., Clinical Team Leader  
Lan Huang, Ph.D., Primary Statistical Reviewer  
Denise Baugh, M.S., OSE Project Manager  
Anthony Mucci, Ph.D., Acting Statistical Team Leader  
Rafel Dwaine Rieves, M.D., Division Director  
Louis Marzella, M.D., Dep. Division Director  
Sharon Thomas, Regulatory Health Project Manager  
Lucie Yang, M.D., Ph.D., Clinical Reviewer  
Jyoti Zalkikar, Ph.D., Statistical Team Leader  
Nicholas Kozauer, M.D., Clinical Reviewer, DNP  
Charles Ganley, M.D., ODE IV, Director  
Karen Fiebus, M.D, Maternal Health Team  
Kaye Kang, PharmD, Chief Project Manager  
Eldon Leutzinger, Ph.D., CMC Team Leader

**SUMMARY:** The Div. Director held an open forum with the team to discuss the AC Meeting held on January 20, 2011. The team discussed the sponsor's topics and additional studies completed after the original NDA submission. ,

**ACTION ITEM:** An Information Request will be forwarded to the sponsor proposing a teleconference to discuss the results of studies, independent review charter, protocols and statistical analysis plan for the re-read.

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/s/  
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SHARON P THOMAS  
02/16/2011



NDA 202008

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Avid Radiopharmaceuticals, Inc.  
3711 Market Street  
Seventh Floor  
Philadelphia, Pennsylvania 19104

ATTENTION: Alan P. Carpenter, Jr., Ph.D., J.D.  
Vice President, Legal and Regulatory Affairs

Dear Dr. Carpenter:

Please refer to your New Drug Application (NDA) dated September 17, 2010, received September 17, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Florbetapir F 18 Injection, 37 MBq/mL to 1900 MBq/mL.

We also refer to your September 27, 2010, correspondence, received September 28, 2010, requesting review of your proposed proprietary name, Amyvid. We have completed our review of the proposed proprietary name, Amyvid, and have concluded that it is acceptable.

The proposed proprietary name, Amyvid, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 27, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Sharon Thomas at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Denise P. Toyer, PharmD.  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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DENISE P TOYER  
12/10/2010

## **DIVISION OF MEDICAL IMAGING PRODUCTS**

### **TEAM MEETING**

**DATE:** November 23, 2010      **TIME:** 11:30 AM      **LOCATION:** 1311

**APPLICATION:** NDA 202-008      **DRUG NAME:** AMYVID (Florbetapir F 18) Injection

**SPONSOR:** Avid Radiopharmaceuticals

#### **FDA ATTENDEES:**

Sunday Awe, Ph.D., Pharm\Tox Reviewer  
Laniyou, Adebayo, Ph.D., Pharm/Tox Team Leader  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Qi Feng, M.D., Primary Clinical Reviewer  
Alex Gorovets, M.D., Clinical Team Leader  
Lan Huang, Ph.D., Primary Statistical Reviewer  
Denise Baugh, M.S., OSE Project Manager  
Anthony Mucci, Ph.D., Acting Statistical Team Leader  
Rafel Dwaine Rieves, M.D., Division Director  
Louis Marzella, M.D., Dep. Division Director  
Sharon Thomas, Regulatory Health Project Manager  
Lucie Yang, M.D., Ph.D., Clinical Reviewer  
Jyoti Zalkikar, Ph.D., Statistical Team Leader  
Nicholas Kozauer, M.D., Clinical Reviewer, DNP  
Ranjit Mani, M.D., Clinical Team Leader, DNP  
Charles Ganley, M.D., ODE IV, Director  
Tammy Howard, R.N., Maternal Health Team  
Kaye Kang, PharmD, Chief Project Manager  
Eldon Leutzinger, Ph.D., CMC Team Leader  
Rajeshwari Sridhara, Ph.D., Dir., Stats

**AGENDA:** Team Meeting (following the Sponsor Presentation Meeting) -Sponsor submitted a revised PI and proposed labeling. The team discussed concerns with the clinicians' ability to interpret/read the images using the "global" read of "positive or negative." The team discussed the 2008 AC recommendation using histopathology as the standard of truth to detect amyloid. The team discussed the sponsor's histopathology data and noted that the sample size were only 14 subjects.

**ACTION ITEM:** Information requests and comments will be forwarded to the sponsor when appropriate.

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SHARON P THOMAS  
02/16/2011

## **DIVISION OF MEDICAL IMAGING PRODUCTS**

### **MID-CYCLE\TEAM MEETING**

**DATE:** November 18, 2010      **TIME:** 1:00 PM      **LOCATION:** 1421

**APPLICATION:** NDA 202-008      **DRUG NAME:** AMYVID (Florbetapir F 18) Injection

**SPONSOR:** Avid Radiopharmaceuticals

#### **FDA ATTENDEES:**

Sunday Awe, Ph.D., Pharm\Tox Reviewer  
Laniyou, Adebayo, Ph.D., Pharm/Tox Team Leader  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Qi Feng, M.D., Primary Clinical Reviewer  
Alex Gorovets, M.D., Clinical Team Leader  
Lan Huang, Ph.D., Primary Statistical Reviewer  
Sandra Griffith, M.S., OSE Project Manager  
Anthony Mucci, Ph.D., Acting Statistical Team Leader  
Rafel Dwaine Rieves, M.D., Division Director  
Louis Marzella, M.D., Dep. Division Director  
Sharon Thomas, Regulatory Health Project Manager  
Lucie Yang, M.D., Ph.D., Clinical Reviewer  
Jyoti Zalkikar, Ph.D., Statistical Team Leader  
Nicholas Kozauer, M.D., Clinical Reviewer, DNP  
Ranjit Mani, M.D., Clinical Team Leader, DNP  
Charles Ganley, M.D., ODE IV, Director  
Tammy Howard, R.N., Maternal Health Team  
Kaye Kang, PharmD, Chief Project Manager  
Eldon Leutzinger, Ph.D., CMC Team Leader  
Rajeshwari Sridhara, Ph.D., Dir., Stats

**AGENDA:** NDA Mid-cycle, Team and Labeling Meeting- To discuss the review status, timeline and labeling of the NDA. EDR submission dated September 17, 2010.

**The Mid-Cycle presentations** were presented by the two Clinical reviewers, Lucie Yang, (Regulatory) and Qi Feng (Efficacy / Safety); Stats, Lan Huang; Clinical Pharmacology, Christy John and Pharm/Tox, Sunday Awe.

**Time-Line:** All reviews due in DARRTS by February 11, 2011

**Labeling:** The team noted that the labeling will require substantial labeling revisions, specifically on how the images should be read. Considerable labeling revisions will also be needed on the reader training manual.

**ACTION ITEM:** FDA to request that the sponsor return for a follow up Sponsor Presentation Meeting and submit a draft a proposed revision to the PI for NDA #202-008.

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/s/  
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SHARON P THOMAS  
02/16/2011

## Thomas, Sharon

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**Subject:** FW: NDA 202-008 Amyvid  
**Importance:** High  
**Attachments:** 1\_Pediatric\_Record.pdf

---

**From:** Greeley, George  
**Sent:** Tuesday, November 16, 2010 12:42 PM  
**To:** Thomas, Sharon  
**Cc:** Salis, Olga  
**Subject:** NDA 202-008 Amyvid  
**Importance:** High

Hi Sharon,

The Amyvid (florbetapir F18) full waiver was reviewed by the PeRC PREA Subcommittee on November 03, 2010.

The Division recommended a full waiver because the disease/condition does not exist in children.

- The PeRC recommended that the Division consider inviting the sponsor to submit a PPSR for this product.

The PeRC agreed with the Division to grant a full waiver for this product. The pediatric record is attached as proof of the PeRC's review.



1\_Pediatric\_Record  
.pdf (62 KB)...

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
10903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: [george.greeley@fda.hhs.gov](mailto:george.greeley@fda.hhs.gov)

 Please consider the environment before printing this e-mail.

## MEMORANDUM OF TELECONFERENCE

**DATE:** October 19, 2010

**TIME:** 11:30 AM-11:45 AM

**LOCATION:** Bldg., 22, Room 2222

**IND/NDA NUMBER(S):** NDA 202,008

**DRUG NAME(S):** AMYVID™ (florbetapir F 18) Injection

**SPONSOR ATTENDEES:** Avid Radiopharmaceuticals

**FDA ATTENDEES:**

Sunny Awe, Ph.D., Non Clinical Reviewer, DMIP

Sharon Thomas, B.Sc.Regulatory Project Manager, DMIP (*Minutes Recorder*)

**SPONSOR ATTENDEES:**

Franz Hefti, PhD, Chief Scientific Officer (for preclinical)

Alan Carpenter, PhD, JD, VP, Legal and Regulatory Affairs

**DISCUSSION:**

On October 18, 2010, the FDA requested a teleconference with the sponsor to discuss if all preclinical studies submitted in the IND were actually included in the NDA with the eCTD links. The sponsor confirmed that all the preclinical studies in IND 79511, including the final reports, were available in the NDA submitted to the FDA. The FDA inquired about the Rhesus Monkey, involving brain uptake conducted at the University of Michigan included in the IND but not in the NDA submission. The sponsor stated that the monkey study is included in a publication (Choi SR, Golding G, Zhuang Z, et al. Preclinical properties of 18F-AV-45: a PET agent for A $\beta$  plaques in the brain. J Nucl Med. 2009;50(11):1887-1894), included in the NDA submission. The meeting concluded at 11:45 am.

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/s/

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SHARON P THOMAS  
10/19/2010

## **FDA-CDER DIVISION OF MEDICAL IMAGING**

### **INTERNAL FILING\TEAM MEETING**

**DATE:** October 14, 2010      **TIME:** 1:00 PM      **LOCATION:** 5266

**APPLICATION:** NDA 202-008      **DRUG NAME:** AMYVID (Florbetapir F 18) Injection

**SPONSOR:** Avid Radiopharmaceuticals

#### **FDA ATTENDEES:**

Sunday Awe, Ph.D., Pharm\Tox Reviewer  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Qi Feng, M.D., Primary Clinical Reviewer  
Alex Gorovets, M.D., Clinical Team Leader  
Lan Huang, Ph.D., Primary Statistical Reviewer  
Sandra Griffith, M.S., OSE Project Manager  
Anthony Mucci, Ph.D., Statistical Reviewer  
Rafel Dwaine Rieves, M.D., Division Director  
Louis Marzella, M.D., Dep. Division Director  
Sharon Thomas, Regulatory Health Project Manager  
Lucie Yang, M.D., Ph.D., Clinical Reviewer  
Jyoti Zalkikar, Ph.D., Statistical Team Leader  
Charles Ganley, M.D., ODE IV, Director  
Anthony Orenca, M.D., DSI Reviewer  
Ravindra Kasliwal, Ph.D., CMC Reviewer  
Eldon Leutzinger, Ph.D., CMC Team Leader

**AGENDA:** NDA Filing, Team Meeting- To discuss timeline, consults and labeling of the NDA. EDR submission dated September 17, 2010.

#### **SUMMARY:**

The NDA is fileable under a Class 1 review with a PDUFA Due Date of March 17, 2011. Consults were confirmed for neurology, microbiology, maternal health and DSI (clinical inspection). The Sponsor's proposed labeling and labels were discussed. It was determined that the label needs significant revisions if approved. FDA comments and information requests will be forwarded to the sponsor when appropriate.

**Minutes Recorded by:** Sharon Thomas, DMIP

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/s/  
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SHARON P THOMAS  
02/16/2011



**NDA 202-008**

**NDA ACKNOWLEDGMENT**

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Florbetapir F18 (18F-AV-45) Injection

Date of Application: September 17, 2010

Date of Receipt: September 17, 2010

Our Reference Number: NDA 202-008

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 16, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Medical Imaging Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, please don't hesitate to contact me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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SHARON P THOMAS  
10/04/2010



IND 79,511

ADVICE/INFORMATION REQUEST

Avid Radiopharmaceuticals, Inc.  
Attention: Alan P. Carpenter, Ph.D.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Florbetapir F 18.

We also refer to your pre-NDA CMC meeting package dated June 22, 2010, containing a brief description of the manufacturing process to be provided in the NDA. We have the following responses to your questions:

**QUESTION 1:**

Are the proposed organization and (b) (4) of Module 3, as described by the Table of Contents, suitable?

**FDA RESPONSE TO QUESTION 1: Yes**

**QUESTION 2:**

Because DS and DP are manufactured (b) (4), and DS is (b) (4), is the proposal to describe the manufacture of DS in the DP manufacturing section, and the proposal to incorporate the specifications, testing and stability of DS in the DP specifications, testing and stability sections, reasonable?

**FDA RESPONSE TO QUESTION 2: Yes**

**QUESTION 3:**

Is the proposal to include the manufacture of DS/DP (b) (4) reasonable?

**FDA RESPONSE TO QUESTION 3:**

Potentially yes, (b) (4) where the composition of the drug product remains the same and complies with the established specifications. Have you verified (b) (4)? Will drug product (b) (4) have

**the same composition (i.e., same formulation), and expected to meet a common set of specifications?**

**QUESTION 4:**

Is the proposed content of manufacturing facility and equipment information reasonable?

**FDA RESPONSE TO QUESTION 4:** No.

You should include the following information in the DMF's for (b) (4):

- a. **Equipment description and principle of operation**
- b. **Equipments specifications**
- c. **Quality system information**
  - **Design controls**
  - **Essential performance standards requirements**
- d. **Design verification testing including programming logic / software testing**
- e. **Safety margin testing**
- f. **Equipment shelf-life**
- g. **Risk assessment including FMECA**
- h. **Functional and electrical testing**
- i. **Bench testing including extraneous environment testing**
- j. **Data for performance verification studies: changes in component parts and operating parameter may need re-verification**
- k. **Compatibility of materials used**

You will need a letter of authorization from each of the contract manufacturers for the DMF's. Each of the manufacturing sites will need a pre-approval inspection, and all facility establishment numbers, noting that some are left vacant, will need to be provided. Also, there must be a statement in the NDA at the time of its submission indicating that all manufacturing sites are ready for inspection (that needs to be verified). For all those sites, you need to provide a complete, accurate address, and the name(s) / telephone / email address or FAX number of contact(s) responsible at that site. Manufacturing site information should be placed in the application in a single location, and easily assessable.

**QUESTION 5:**

Is the proposed strategy for DS/DP process validation reasonable?

**FDA RESPONSE TO QUESTION 5:**

The NDA should include validation methods and brief summaries of results for sterilization and depyrogenation processes conducted at the PET manufacturing sites. Materials sterilized by vendors should have a certificate of analysis identifying them as sterile and a qualification plan to ensure material sterilization.

**QUESTION 6:**

Are the proposed release specifications and PQITs for DS/DP reasonable?

**FDA RESPONSE TO QUESTION 6:**

Yes, generally, for attribute and acceptance criterion. However, be advised that this response is only preliminary, and the applicability and appropriateness of each attribute and acceptance criterion will be evaluated again during review of the NDA on submission.

**QUESTION 7:**

Are the proposed DS/DP test methods (common DS/DP-specific methods; equivalent other test methods) and validation reasonable?

**FDA RESPONSE TO QUESTION 7:**

For those methods indicated as “equivalent” for comparison between CMO’s, you will need to demonstrate in the validation information that any differences in methods between any CMO’s will not impact analytical results, compared with results from methods that would be otherwise identical. The issue here is that a uniform product will be produced at each of the CMO’s involved, and will meet a common set of specifications.

For specific activity, we note that it is proposed as a (b) (4). If a (b) (4) is to be used, (b) (4), it needs to be fully validated as applicable and to produce accurate values for specific activity and mass dose. However, we recommend that this determination be made using a standard curve.

Also, be advised of the following. As well as impurities, both radioactive and non-radioactive, we are concerned that in the identification of the drug molecule (radiochemical identity), the HPLC retention times will be unique for [<sup>18</sup>F]FIAU and FIAU standard, and based on the analytical methodology the risk of administration of product containing the wrong drug molecule will be miniscule.

**QUESTION 8:**

Is the proposed microbiological information (procedures, testing and validation) reasonable?

**FDA RESPONSE TO QUESTION 8:**

The following information should be included in the NDA. This is not an exhaustive list and additional sterility assurance information may be required depending on the manufacturing processes and manufacturing facilities.

- a. A complete list of manufacturing facilities at which Florbetapir F 18 will be manufactured
- b. A description of the (b) (4) processing areas for each facility
- c. The location of equipment used for processing the drug solution
- d. A description of the program to be used to demonstrate environmental control of the manufacturing area.
- e. A description of all sterilization methods to be used at the manufacturing facilities
- f. A statement as to whether or not the drug product will be re-processed (e.g., in the event of a failed filter bubble point test).

**QUESTION 9:**

Is the proposed stability data package for DS/DP reasonable?

**FDA RESPONSE TO QUESTION 9: No.**

You are saying that bulk drug product will be (b) (4) (b) (4)

[Redacted text block]

**We suggest that an appropriate stability matrix be designed to cover all of the proposed vial and syringe products to be distributed.**

**QUESTION 10:**

Is the proposal for Environmental Assessment exemption reasonable?

**FDA RESPONSE TO QUESTION 10: Yes.**

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-79511	GI-1	AVID RADIOPHARMACE UTICALS INC	18 F AV 45

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/

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SHARON P THOMAS  
08/09/2010

## FDA Preliminary Responses

**Introductory Comment:** This material consists of our preliminary responses to your questions in preparation for the discussion at the meeting scheduled for July 19, 2010, at 3:00 p.m. EST, between **Avid Radiopharmaceuticals, Inc.** and the **Division of Medical Imaging Products (DMIP)**. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we expect you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. If you choose to cancel the meeting, this document will represent the official record of response to your questions. If you determine that discussion is needed, please indicate the items from the original questions you would like to have clarified. If there are any major changes to your development plan, the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. Please note that Avid will be responsible for providing a verbal summary of the key discussion points, agreements and action items at the close of the meeting.

### **QUESTIONS TO THE AGENCY**

#### *Nonclinical Pharmacology and Toxicology:*

1. Is the proposed organization of Module 4, as described by the eCTD Table of Contents, suitable?

#### **FDA Response:**

For information re: eCTD format and submission, please refer to <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf>. If you have additional questions, you may contact The Office of Training and Communications (301-796-0597) or [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov).

2. Is the pharmacology information supportive of the proposed indication for use?

#### **FDA Response:**

This is a review issue. It is premature to make determination on whether the pharmacology information supports the proposed indication.

3. Does the Agency recommend that supportive non-clinical pharmacology information be included in the ISE and annotated PI?

**FDA Response:**

**No. It is not necessary to include the supportive non-clinical pharmacology information in the ISE. However, the non-clinical pharmacology information required for the appropriate sections of the labeling should be provided.**

4. Is the proposed nonclinical safety pharmacology and toxicology information sufficient for review?

**FDA Response:**

**The Agency would have to review the submission before the adequacy of the nonclinical safety pharmacology and toxicology information can be determined. It is therefore premature to make such determination.**

5. Does the Agency require a formal request for waiver of carcinogenicity studies?

**FDA Response:**

**Yes. A formal request with justification is required for a waiver of carcinogenicity studies by the Agency.**

***Clinical:***

6. Does the agency agree with the presentation and analysis of the pivotal phase III (A07) trial data (summarized starting on page 59 of the Briefing Document)

**FDA Response: Yes, we generally agree. However, we have additional requests which we list in response to your Question 7.**

7. Are there other presentations of the A07 trial data or additional analyses that the agency requires or recommends for the NDA?

**FDA Response:**

**The presentations and analyses in the submitted Meeting package are incomplete, in terms of the extent of information needed within a marketing application. When submitting your application please include tables and derived data sets represented below. Both the tables and the data sets must contain individual reader results, not just median and majority results.**

**A. The Statistical Reviewer requests the following Table for the 29 Autopsy Subjects**

Subject ID	Primary Semi-Quantitative Scores		Qualitative Classification A $\beta$ + = 1; A $\beta$ - = 0		SUVR	IHC	Autopsy AD Status
	Three Reader Scores	Median Score	Three Readers	Majority			
#1	A=; B=; C=		A=; B=; C=				

#2							
#29							

Also: For the semi-quantitative Scores  
The following three tables of frequencies: (Z1, Z2) = (A, B), (A, C), (B, C)

	Reader Z2 = 0 or 1	Reader Z2 = 2	Reader Z2 = 3 or 4
Reader Z1 = 0 or 1			
Reader Z1 = 2			
Reader Z1 = 3 or 4			

**B. the Statistical Reviewer requests the following Derived Data Sets**

One line of data per Subject

**First Set of Variables:**

Subject ID, Age, Race, Gender, Weight, APoE Status

**Second Set of Variables**

Cohort, Cognitive Status at Screening (Could be more than one result)

Also, for End-of-Life Cohort: =1 if used in Specificity calculations; =0 otherwise

**Third Set of Variables (where Applicable)**

IHC Result, NIA Reagen, CRAD, Autopsy classification as AD/not AD

**Fourth Set of Variables (In End-of-Life Cohort Reads):**

SUVR; Semi-Quantitative Score and Binary classification for each Reader

**Fifth Set of Variables: (For each Reader in Specificity Reads)**

Binary Classification

- Does the Agency have any comments on the proposed ISS or ISE Table of Contents or any requests for the format or data to be included in the ISS, ISE or Module 2 summaries?

**FDA Response:**

**Please see our response to Question 7.**

- Is the pediatric study waiver request reasonable?

**FDA Response:**

**Yes, it appears to be reasonable for submission.**

10. Is the safety population sufficient for filing and review?

**FDA Response:**

**From your Meeting Package, we understand that a total of 496 human subjects have received the tracer injection. Such a population appears sufficient based on the supplied information. The final determination of sufficiency will be based upon the review findings.**

11. SAS datasets for clinical studies will be provided in lieu of case report tabulations in accordance with the "Guidance for Industry – Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)" and "Study Data Specifications (v1.5.1, January 2010)". Each dataset will be submitted as a SAS transport file in accordance with the above referenced guidance/specification. Separate Patient Profiles are not planned to be submitted. Does the Agency agree with this approach?

**FDA Response:**

**Yes, we agree.**

12. Avid proposes to include individual subject CRFs only for deaths and drop-outs in the NDA. Is this viewed by the Agency as a reasonable approach?

**FDA Response:**

**No. We do not agree. You need to provide CRFs of all AEs, including SAE and deaths, as well as all drop-outs.**

13. Are there any other issues associated with the Clinical eCTD contents which the Agency wishes Avid to address?

**FDA Response: No.**

***eCTD Format and Submission:***

14. Does the Agency have any special requests or suggestions on the format or method of submission of an electronic CTD?

**FDA Response: Please see response to #1 above.**

15. Does the Agency wish to have a reviewer training set up for the review of the florbetapir F 18 NDA in eCTD format?

**FDA Response: No.**

16. The NDA will be submitted in eCTD format according to the latest FDA guidance and specifications. (b) (4) will generate the eCTD submission. Since (b) (4) has successfully submitted a pilot eCTD submission (reference eCTD pilot 90024; June 2004), Avid requests a waiver for the requirement to submit a pilot eCTD submission. Does the Agency agree?

**FDA Response:**

**Please contact The Office of Training and Communications regarding waiver requirements on a pilot eCTD submission.**

17. At this time, does the Agency note any deficiencies in the proposed submission contents that would impair the review of the NDA?

**FDA Response: No, we do not note deficiencies at this time based on the supplied information.**

**Additional FDA Comments:**

- 1. In your application, provide a detailed description of the semi-quantitative scoring methodology and specifically of the reader training as it related to this methodology. We are particularly concerned about the guidance to be provided to clinical interpreters within the package insert or other marketing information. Within the application, focus upon drawing an explicit description of the guidance provided to image interpreters in Study A07 and how this guidance is similarly conveyed within the proposed marketing information (package insert or other document).**
- 2. In your application, when submitted, provide a detailed description of the qualitative image assessment methodology and specifically of the reader training as it related to this methodology. Please confirm that this methodology was the same for all subjects in the study, regardless of the cohort of origin or the analysis.**
- 3. Please clarify whether any of the images were also interpreted at a study site.**
- 4. Please provide information regarding drug interaction potential with concomitant drugs used in AD patient population as requested earlier by the Agency.**

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND-79511

GI-1

AVID  
RADIOPHARMACE  
UTICALS INC

18 F AV 45

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/s/  
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SHARON P THOMAS  
07/15/2010

**Thomas, Sharon**

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**From:** Thomas, Sharon  
**Sent:** Saturday, May 29, 2010 9:34 AM  
**To:** 'Alan Carpenter'  
**Cc:** 'David Haenick'  
**Subject:** RE: Dr. Carpenter: IND 79511 [F-18-AV-45] Florbetapir: FDA Meeting - Thursday, July 15, 2010 at 12:30 - 2:30 pm, EST (re: Meeting Request dated 05/10/10)

Dear Dr. Carpenter,

As indicated below in Ms. Nguyen's email, I have been reassigned as the new Project Manager to your IND. We have the following dates available for your preNDA Meeting Request submitted on May 10th:

- 1) **Wednesday, June 30, 2010 - 2:00 - 3:30 pm (the Meeting Package must be available by Wednesday, June 2, 2010)**
- 2) **Monday, July 19, 2010 - 3:00 - 4:30 pm (the Meeting Package must be available by Friday, June 18, 2010)**
- 3) **Thursday, August 26, 2010- 2:30 - 4:00 pm (the Meeting Package must be available by Monday, July 26, 2010)**

Please confirm one of the dates above and should you have any questions please don't hesitate to contact me.

Thank you,

Sharon Thomas  
Project Management Staff  
Division of Medical Imaging Products  
(301) 796-2050 (o)  
(301) 796-9849 (f)

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**From:** Nguyen, Thuy M  
**Sent:** Thursday, May 27, 2010 1:06 PM  
**To:** Alan Carpenter  
**Cc:** 'David Haenick'; Thomas, Sharon  
**Subject:** RE: Dr. Carpenter: IND 79511 [F-18-AV-45] Florbetapir: FDA Meeting - Thursday, July 15, 2010 at 12:30 - 2:30 pm, EST (re: Meeting Request dated 05/10/10)

Dear Dr. Carpenter,

Regarding IND 79511, it has been reassigned to a new Project Manager: Ms. Sharon Thomas, and she will inform you shortly of the new meeting date.

If you have any questions regarding IND 79511, please contact Ms. Thomas at (301) 796-2050.

Sincerely,  
Thuy Nguyen

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**From:** Nguyen, Thuy M

2/15/2011

**Sent:** Wednesday, May 26, 2010 9:23 AM

**To:** Alan Carpenter

**Cc:** 'David Haenick'

**Subject:** Dr. Carpenter: IND 79511 [F-18-AV-45] Florbetapir: FDA Meeting - Thursday, July 15, 2010 at 12:30 - 2:30 pm, EST (re: Meeting Request dated 05/10/10)

**Importance:** High

Dear Dr. Carpenter,

Regarding IND 79511 [F-18-AV-45], per your email correspondence, 05/25/10, the meeting scheduled on July 15, 2010, to discuss pre-clinical and clinical data will be rescheduled with consideration to the alternate dates you have suggested.

I will inform you of the new meeting date when it becomes available.

Sincerely,  
Thuy Nguyen

---

**From:** Alan Carpenter [mailto:carpenter@avidrp.com]

**Sent:** Tuesday, May 25, 2010 7:57 PM

**To:** Nguyen, Thuy M

**Cc:** David Haenick

**Subject:** RE: Dr. Carpenter: IND 79511 [F-18-AV-45] Florbetapir: FDA Meeting - Thursday, July 15, 2010 at 12:30 - 2:30 pm, EST (re: Meeting Request dated 05/10/10)

**Importance:** High

Dear Ms. Nguyen,

Thank you for the response to our meeting request. [REDACTED] (b) (6)

[REDACTED] Avid would be agreeable to meet with the Agency during the following week, specifically any of the days of Tuesday July 20 through Friday Jul 23 or the following week of July 26. We sincerely regret the difficulty this scheduling conflict presents and will be agreeable to any time during this period which is acceptable to FDA.

We will also contact Rebecca McKnight to discuss a separate CMC-Microbiology meeting.

Please let me know if you would like to discuss this on the phone.

Sincerely,

Alan Carpenter

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Alan P. Carpenter, Jr., Ph.D., J.D.  
Vice President, Legal & Regulatory Affairs  
Avid Radiopharmaceuticals, Inc.  
3711 Market Street, 7th Floor  
Philadelphia, PA 19104  
phone: (215) 298-0707  
cell: (857) 928-4520  
[www.avidrp.com](http://www.avidrp.com)  
[carpenter@avidrp.com](mailto:carpenter@avidrp.com)

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**From:** Nguyen, Thuy M [mailto:Thuy.Nguyen@fda.hhs.gov]  
**Sent:** Tuesday, May 25, 2010 6:17 PM  
**To:** Alan Carpenter  
**Subject:** Dr. Carpenter: IND 79511 [F-18-AV-45] Florbetapir: FDA Meeting - Thursday, July 15, 2010 at 12:30 - 2:30 pm, EST (re: Meeting Request dated 05/10/10)

Dear Dr. Carpenter,

Regarding IND 79511: [F-18-AV-45] Florbetapir, **Meeting Request submission dated May 10, 2010, a Type B Pre-NDA Face-to-Face Meeting** is scheduled for Thursday, July 15, 2010, at 12:30 - 2:30 pm, EST, to discuss pre-clinical and clinical data with regards to submitting an eCTD NDA.

Submit the Meeting Package by June 15, 2010, along with the Dial-In #, and if applicable, the Foreign Visitor Data Request Form - See attached Meeting Letter, 05/25/10, which you will also receive by postal mail.

For a separate CMC-Microbiology meeting, please contact Ms. Rebecca McKnight, ONDQA - CMC Project Manager, to submit a meeting request directly to ONDQA-CMC: [Rebecca.McKnight@fda.hhs.gov](mailto:Rebecca.McKnight@fda.hhs.gov) or (301) 796-1765.

If you have any questions, please feel free to contact me.

Sincerely,  
Thuy Nguyen  
Senior Regulatory Health Project Manager  
FDA CDER - Division of Medical Imaging Products  
(301) 796-2050

**\*CONFIDENTIAL**

**FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

**TO: David Haenick, R.Ph., Ph.D.  
Avid Radiopharmaceuticals, Inc.  
Office: (215) 298-0718  
Email: Haenick@avidrp.com**

**Regarding IND 79511 [F-18] Florpiramine, email correspondence of March 16, 2010, the FDA has the following CHEMISTRY Comments – April 15, 2010.**

**Reminder: All correspondences\submissions regarding IND 79511, should be submitted to the FDA in *triplicate* hard copies with a cover letter, Form FDA 1571, along with an electronic copy on CD-Rom (PDF), as follow:**

**Rafel Dwaine Rieves, M.D., Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Attention: FDA Central Document Room (CDR)  
5901-B Ammendale Rd  
Beltsville, MD 20705-1266**

**If you have any questions, please feel free to contact me.**

**FDA CHEMISTRY COMMENTS**

Regarding your email correspondence dated March 16, 2010, the FDA has the following Chemistry Comments:

The Environmental Assessment (EA) is for the PET drug. But, the structure of the non-radioactive part of the PET drug comes from the precursor (AV-105), so needs to be considered within the EA. Consult the FDA website for guidance on EA:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>

The guidance contains a formula for calculating the estimated concentration of the substance at the point of entry into the aquatic environment. If that estimate amounts to less than 1 ppb, the NDA will qualify for a categorical exclusion. So, the Sponsor should read the above indicated guidance carefully and follow that for EA requirements in preparation of the NDA.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-79511

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ORIG-1

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AVID  
RADIOPHARMACE  
UTICALS INC

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/s/

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THUY M NGUYEN  
04/15/2010

**\*CONFIDENTIAL**

**FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS**

**May 18, 2009**

**Dear Dr. Alan Carpenter, Ph.D., J.D.**  
**Vice President, Legal & Regulatory Affairs**  
**Avid Radiopharmaceuticals, Inc.**  
**Office: (215) 966-6173**  
**Email: [carpenter@avidrp.com](mailto:carpenter@avidrp.com)**

**Regarding IND 79511: [F-18] AV-45, attached is the FDA Preliminary Meeting Response, May 18, 2009, to the Meeting Package dated April 21, 2009.**

**Please review and let me know (via email) by 9:00 am, EST, Wednesday, May 20, 2009, if Avid still wishes to have the teleconference at 12:00 – 1:00 pm, EST, May 21, 2009.**

**If so, specify (in order of preference) which specific Meeting Questions / Responses Avid would like to discuss.**

**Please do not present new information / data during the teleconference since the FDA would not have had adequate review time.**

**If you have any questions, please feel free to contact me.**

**Sincerely,**  
**Thuy Nguyen**  
**Regulatory Health Project Manager**  
**FDA – Division of Medical Imaging and Hematology Products**  
**(301) 796-2050**

## FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

IND 79511: [F-18] AV-45

Sponsor: AVID

Type C: Teleconference

### FDA Preliminary Meeting Response, 05\18\09, to the Meeting Package of 04\21\09

Below are the FDA preliminary responses\comments in preparation for the teleconference on May 21, 2009, and may not be fully vetted internally and should not be considered as an official position of the FDA. It is shared with the Sponsor solely to promote a collaborative and successful discussion during the teleconference. The FDA teleconference minutes will reflect agreements and discussion and might not be consistent with these preliminary responses\comments.

#### **SPONSOR MEETING QUESTION #1**

*Under the current IND and in this background package Avid has proposed specifications for the drug substance (DS). However, since the drug substance is* (b) (4)

*, these specifications for DS are only based on testing of the DP. Does the Agency prefer for Avid to have separate specifications listed for DS and DP (as Avid currently proposes) even if the DS is not tested itself?*

#### **FDA CMC RESPONSE #1**

For a radiopharmaceutical drug substance (b) (4), there is no advantage to having a separate set of specifications for DS and DP. Specifications for DP are sufficient. However, if you intend to have separate specifications for both DS and DP, we have no objection.

**SPONSOR MEETING QUESTION #2**

*AVID's current IND specifications and the proposed NDA drug product specifications are included in the appendix material.*

- A. Are the AVID proposals for drug substance and drug product specifications (Appendices 9 and 10) reasonable?*
- B. Is the proposal for precursor specifications (Appendix 11) reasonable?*

**FDA CMC RESPONSE #2**

Except as noted under CMC Response #12A, tentatively, they appear reasonable, but will be reviewed again when the full NDA is submitted.

**SPONSOR MEETING QUESTION #3**

*AVID proposes to perform identification testing of excipient ethanol and excipient / (b) (4) sodium ascorbate in the drug product prior to release. Does the Agency agree that this is sufficient for a PET drug such as Floripiramine F 18?*

**FDA CMC RESPONSE #3**

Yes, from a CMC perspective.

**SPONSOR MEETING QUESTION #4**

*For purposes of process validation, AVID proposes that the GMP process (Appendix 7)*

(b) (4)  
[Redacted text]

**FDA CMC RESPONSE #4**

No. (b) (4)  
[Redacted text]

**SPONSOR MEETING QUESTION #5**

*For purposes of AV-105 process verification, AVID proposes to submit batch release data meeting specifications for 3 batches (1 non-CMP batch and 2 GMP batches) at proposed commercial scale [REDACTED] (b) (4) (example data in Appendix 8). Is this acceptable?*

**FDA CMC RESPONSE #5**

This is a GMP issue, and ultimately its acceptability will depend on an assessment at the time of the inspection. Understand that the purpose of process verification is to demonstrate that the process (here we are talking about a new process) for producing the PET drug product is reproducible and capable of producing the product meeting the established acceptance criteria. In that context, you need to assess whether 2 GMP batches will adequately provide the necessary demonstration of reproducibility.

**SPONSOR MEETING QUESTION #6**

*For purposes of manufacturing site and equipment [REDACTED] (b) (4), validation for the NDA, AVID proposes to manufacture drug product that meet specifications for 3 consecutive validation batches at each manufacturing site (~ 10 sites) in accordance with final NDA processes and QC methods. A) Is this degree of validation acceptable? B) If three batches cannot be completed for a given manufacturing site by the time of NDA submission, will it be acceptable if AVID commits to completion of 3 consecutive successful validation batches prior to commercial production in accordance with a validation protocol to be included in the NDA?*

**FDA CMC RESPONSE #6**

A. Yes. Batch data and testing results for each of the consecutive validation batches should be available for examination during CGMP inspection of each manufacturing site.

B. No. All manufacturing sites will need to undergo a PAI, and must be ready for inspection at the time of submission of the NDA, if they are to be included in those sites to produce and distribute product under the NDA when approved. "Ready for inspection" includes a minimum of 3 consecutive validation batches to demonstrate consistency of the process as part of the determination of whether a given site is CGMP compliant. If the minimum number of consecutive validation batches have not been produced, and the requisite data is not available to the inspector at the time of the inspection, the site is at risk for being considered not ready for inspection. The consequences may result in delays in the approval of the NDA if all sites are to be included. Any manufacturing sites to be added during the IND, and prior to the NDA, should be included in amendments to the IND. Any sites to be added after approval of the NDA will need to be via supplement.

**SPONSOR MEETING QUESTION #7**

*Are the proposed stability programs for precursor (Appendix 12) and drug product (Appendix 13) acceptable?*

**FDA RESPONSE #7**

**CMC RESPONSE**

Yes, except for the following considerations. You have not specified the number of batches that will be included in the stability studies for drug product. There is absence of information on the strength of the batches to be included. Also, at least at one of the sites, stability should be assessed at the highest radioactivity concentration (at the highest anticipated activity level) that will be produced and packaged in the intended container closure system. Be advised that this is contingent on the degree of similarity of production and controls at each of the sites that will manufacture commercial product. Factors to be considered include, e.g., (a) same type of equipment, (b) same materials (source and purity / quality), (c) uniformity in the purity and quality of the precursor, (d) same analytical testing procedures, (d) same specification limits.

**MICROBIOLOGY RESPONSE**

Based upon the information provided, the microbiology tests in the proposed stability programs appear acceptable.

**SPONSOR MEETING QUESTION #8**

*Are the proposed analytical and microbiological methods and validation plans for the NDA reasonable (See analytical method summaries for precursor and DP in Appendices 14 and 15 and method validation plans in Appendix 16)?*

**FDA RESPONSE #8**

**CMC RESPONSE**

The general plan looks acceptable. However, the final determination of the adequacy of the analytical procedures will depend on review of the procedures used in their validation and the validation data when that information is submitted with the NDA. We recommend that you consult ICH Q2(R1) [Q2A and Q2B] for guidance on validation of analytical procedures, found at the FDA website. The address of the FDA website is <http://www.fda.gov/cder/guidance/index.htm>. You should also consult the "Reviewers Guidance, Validation of Chromatographic Methods" at the FDA website. The address of this website is <http://www.fda.gov/cder/guidance/index.htm#chemistry>.

**MICROBIOLOGY RESPONSE**

Based upon the information provided, the proposed microbiological methods appear adequate. Note that endotoxin method validations should be conducted using three lots of drug product.

**SPONSOR MEETING QUESTION #9**

*The current IND specifications and proposed NDA characterization methods for reference standards are outlined in Appendix 17. Does the Agency have any comments with respect to the proposed characterization of reference standards?*

**FDA CMC RESPONSE #9**

Because identification of the drug molecule is indirect, the authenticity of the reference standard is considered critical, and the information provided in the NDA will be reviewed in depth. To this end, we request that all chromatograms and spectra be legible and fully interpreted by AVID. For chromatograms, the peaks should be identified as to which is due to the drug molecule and which is due to the precursor, and how these assignments are known / made. All impurity peaks need to be discussed, including their significance (if any). Any unusual peaks / events (e.g., shoulders, split peaks, ghost peaks or other artifacts) should be discussed with their potential significance. The reference standard should be of the highest purity achievable, within what is technically possible, given the state of the art. Spectra (e.g., NMR) should be fully interpreted; resonance signals ( $^1\text{H}$  /  $^{13}\text{C}$ ) should be identified as to which protons / carbons in the assigned structure they correspond. There are similar considerations for other spectra that may be submitted (e.g., MS).

**SPONSOR MEETING QUESTION #10**

*A draft outline has been prepared for the planned Module 3 to be filed in eCTD format (See Appendix 1). Does the Agency have any comments or suggestions with respect to the proposed organization of this Module 3 outline (e.g., the proposed organization for precursor and drug substance)?*

**FDA CMC RESPONSE #10:**

No.

**SPONSOR MEETING QUESTION #11**

*In the Description of Manufacturing Facilities (see Appendix 1, CTD Module 3, appendix sections 3.2.A.1), AVID proposes to include the company, site name, address, FDA Establishment Number, and description of site-specific material flow during drug product manufacture. Is this an appropriate level of information for this section?*

**FDA RESPONSE #11**

**CMC RESPONSE**

No. You also need to include a CFN / FEI number, and a contact person for each site listed, along with their telephone number and email address. Also, for the NDA, you need to include a statement in this section (Module 3) whether this site is “ready for inspection.”

**MICROBIOLOGY RESPONSE**

In addition, please provide a detailed description of the production areas and the environmental controls (e.g., laminar air flow hoods, biosafety cabinets, isolators) that protect product components from microbiological sources of contamination.

**SPONSOR MEETING QUESTION #12**

*What other recommendations does the Agency have with respect to the proposed NDA information and contents for CMC manufacturing and quality control?*

**FDA RESPONSE #12**

**CMC RESPONSE**

A. We have noted under Floripiramine F 18 Injection Release Specifications (page 42) that the acceptance criterion for radiochemical identity by HPLC is a relative retention time of [REDACTED] <sup>(b) (4)</sup> with respect to the reference standard. We have the following comments:

We are concerned that the QC procedures used in determining radiochemical identity have the capability to exclude the possibility that a ‘wrong’ drug molecule will wind up in the finished drug product, and that this can be assured on a routine basis. To this end, the retention time for the drug molecule should be sufficiently unique, so that the risk for a wrong drug substance molecule to be mistaken for [<sup>18</sup>F]AV-45 is negligible. In view of these concerns, we continue to recommend co-injection whenever that is feasible or warranted. If it is not feasible or warranted, the justification needs to rest on sound science; whatever procedure is used needs to be fully validated to be suitable for the intended purposes.

CMC RESPONSE #12 (cont.)

B. Since there will be 10 manufacturing sites involved under this IND, be advised that the sponsor (AVID) is ultimately responsible for the product produced at all of the manufacturing sites, and should have a defined and written plan in place, managed by AVID, to ensure that product produced at all the sites will meet the established specifications. Additionally, any change in materials, methods, analytical procedures, etc., should be reviewed and approved by AVID before implemented. To this end, AVID should have a Change Control Protocol in place that will specify and delineate the process to be used in making any change at any one of the manufacturing sites. We expect that this Change Control Protocol will be in the NDA at the time of its submission.

MICROBIOLOGY RESPONSE

The NDA should also contain the following product quality microbiology information:

- The maximum dose and volume to be delivered per patient (for endotoxin limit calculations).
- The drug product storage conditions (time and temperature) prior to administration.
- The number of doses per vial.
- A description of the final container closure system. All components should be sterile. Multi-use vials will require studies to validate the storage conditions
- Equipment sterilization validation.
- The results of at least (b) (4) processing simulations conducted on each proposed (b) (4).

Additional information can be found in the 1994 *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

**SPONSOR MEETING QUESTION #13**

*Given the expectation that 21 CFR Part 212 will govern the manufacture of PET drugs in the future, what effect would the issuance of CFR 212 have on AVID's NDA application if the regulation was issued either shortly before or during the FDA review of the application? Can the FDA comment if there will be a phase-in period for the implementation of CFR 212?*

**FDA CMC RESPONSE #13**

The final rule has not yet been published. Until then, USP <823> is required (Section 501(a)(2)(c)) for all PET producers. This section will expire 2 years after publication of the final rule on CGMP's for PET drugs. After that time, PET drugs to be marketed under approved NDA's cannot comply with the CGMP's for PET drugs by following USP <823> only, and must comply with 21 CFR 212. There will be a 2 year phase-in period in which to come into compliance with the CGMP's for PET drugs. Note that many of the concepts and principles of USP <823> are incorporated into 21 CFR 212. CGMP inspection of PET facilities will take into consideration the requirements appropriate to PET drugs.

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 79511

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AVID  
RADIOPHARMACEUTIC  
ALS INC

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18 F AV 45

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/

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THUY M NGUYEN  
05/18/2009



**AGENDA:** To discuss the FDA Preliminary Meeting Response of February 6, 2009, with regards to the Sponsor Meeting Package of January 9, 2009 - See Attachment #1, and to the Sponsor's Reply to the FDA Meeting Response – See submission dated 02\09\09.

Following the introduction of participants, the Sponsor stated that Avid agreed with the FDA Meeting Response of 02\06\09. However, the following Meeting Responses were discussed:

**FDA Meeting Response #1.2a:** The Sponsor asked if their proposed approach (see submission dated 02\09\09) is appropriate to which the Division replied yes, however, interpreting the scans should be unbiased and the Sponsor needs to address the interpretation bias.

**FDA Meeting Response #1.2b:** The FDA has no objections to the Sponsor using the Spearman's Correlation analysis as long as the software can handle the "ties" in the data. The FDA requested that Sponsor also provide the regression plots.

**FDA Meeting Response #1.2d:** The Sponsor stated that visual and quantitative reads will be done. The Sponsor will also conduct secondary analyses based on SUVr data as additional exploratory analyses.

**FDA Meeting Response #1.2e:** The FDA is concern with the treatment of the "uninterpretable" scans and suggested that the Sponsor exclude only those images where all (3) blinded-readers agreed on the reason why the image was uninterpretable. The Sponsor will specify the reasons for scoring an image as "uninterpretable".

**FDA Meeting Response #2.c.ii:** The Sponsor agreed to implement the FDA's suggestion regarding the median read.

In conclusion, the Sponsor will submit a revised protocol and a preliminary charter in a few weeks.

**TCON MINUTES RECORDED BY:** T.Nguyen, DMIHP

**ATTACHMENT #1**

**FDA - DIVISION OF MEDICAL IMAGING AND  
HEMATOLOGY PRODUCTS**

IND 79,511: [F-18] AV-45

Sponsor: AVID

Type C: Industry Meeting

FDA Preliminary Meeting Response, 02\06\09, to the Meeting Package of 01\09\09

**SPONSOR MEETING QUESTION #1**

*Does the Agency find the proposed hypothesis and associated analytical methods reasonable for evaluating the correlation of florpiramine F 18 PET images and histopathology?*

**FDA RESPONSE #1**

No, we do not fully agree. Whereas we concur with your objective to establish a correlation between imaging and histopathology observations, we request that, in addition, you demonstrate high specificity of florpiramine F 18 PET images in detection/exclusion of brain amyloid.

We therefore recommend that your design satisfy the following two conditions (with statistical significance):

1. There should be a statistically significant correlation between amyloid levels on histopathology and amyloid levels on F-18 PET. It would be preferable, of course, for the amyloid levels established through reads of the PET images to agree exactly with the levels determined by histopathology, but it is acceptable to simply obtain a positive correlation between these reads.
2. There should be a reasonably larger sample of normals (five is too small) in whom PET reads show no amyloid. These normals will not, of course, undergo autopsy, but their profiles should clearly and strongly suggest an absence of amyloid.

**FDA RESPONSE #1 (cont.)**

We have additional comments:

- a) The subjects studied to satisfy condition 1 (autopsy cohort) are intended to be distinct from those studied to satisfy condition 2 (normal cohort). The five normal subjects cited in the current protocol can be part of the latter population as can be amyloid negative patients from the autopsy cohort. We also recommend that you consider lowering the age limit for enrolling subjects in the autopsy cohort so that a higher proportion of subjects in that cohort might be amyloid-negative.
- b) You propose to use Spearman's correlation to assess condition 1. This raises a problem since you intend to treat the reader results as categorical rather than continuous. Please clarify the reasons you have made this choice, and the reasons you have apparently decided to disregard the incompatibility of such an approach with the usual Spearman's requirement of continuous observations.
- c) We note that no criteria have been included regarding the manner in which the reader results will be combined. Here are two possibilities:
  - i. Two of the three readers must simultaneously satisfy condition 1 and condition 2.
  - ii. The median read (amyloid level over three reads) should satisfy condition 1 and the majority read (presence/absence of amyloid) should satisfy condition 2.
- d) Please justify the use of a subjective scale (rather than SUVs, for instance) for the primary analysis comparisons
- e) It is apparently assumed that all the F-18 PET images are interpretable. Confirm that this is the expectation, or, if uninterpretables can occur, provide an imputation scheme for handling them.

**FDA RESPONSE #1 (cont.)**

f) We consider the following secondary analysis to be useful:

The readers could score each of the six regions for % amyloid, and these results could be compared to the regional histopathology results. This approach does not increase sample size by much, since the regional results are presumed to be highly correlated. However, it could provide a more informative regression between histopathology and F-18. Here's why:

Suppose there were two regions, A and B. Suppose:

Histopathology gives 70% amyloid to A, 0% to B

F-18 gives 40% to A, 30% to B

Then, globally, histopathology and F-18 match perfectly, masking F-18's Specificity failure on B. Further, this analysis could provide Specificity results even on patients who, globally, are positive for amyloid, but who have amyloid free regions.

Provide a revised protocol and the statistical analysis plan to the agency for review and comments.

**SPONSOR MEETING QUESTION #2**

*Does the Agency agree with the proposed study design?*

**FDA RESPONSE #2**

Please see FDA Response #1.

**SPONSOR MEETING QUESTION #3**

*Does the Agency suggest alternative/additional analyses to be conducted?*

**FDA RESPONSE #3**

Please see FDA Response #1.

**SPONSOR MEETING QUESTION #4**

*Does the Agency agree that reaching the primary endpoint of the proposed Phase 3 trial with statistical significance is appropriate for demonstrating the effectiveness of florpiramine F 18 PET for its proposed indication?*

**FDA RESPONSE #4**

No, we do not agree.

Your currently-proposed indication as stated in this submission is as follows:

[REDACTED] (b) (4)

While reaching the primary study endpoint (at a statistically significant level) might be sufficient to demonstrate that florpiramine F 18 positron emission tomography can image amyloid deposits in the brain, it cannot demonstrate that the same imaging technique can [REDACTED] (b) (4) To establish the latter, a study of a different design will be needed.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 79511

AVID  
RADIOPHARMACEUTIC  
ALS INC

18 F AV 45

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/s/

THUY M NGUYEN

03/04/2009